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In chronic sodium depletion the glomerular filtration rate may be reduced, and alterations in proximal tubular function may contribute to the maintenance of antinatriuresis. Measurements were made by micropuncture technique in superficial nephrons of the Munich-Wistar rat of (*a*) the determinants of glomerular filtration rate, (*b*) peritubular capillary hydrostatic and oncotic pressure, and (*c*) proximal tubular fractional and absolute reabsorption in both a control group (group 1, n = 12) and a group of chronically sodium-depleted rats (group 2, n = 12). Single nephron filtration rate (sngfr) was 37.2±1.2 in group 1 and 31.6±1.0 nl/min/g kidney wt ($P < 0.05$) in group 2. Of the factors potentially responsible for the observed reduction in sngfr, there was no change in systemic oncotic pressure or the transglomerular hydrostatic pressure gradient. Sngfr was lower in group 2 because of both a reduced single nephron plasma flow (rpf) (128±6 vs. 112±5 nl/min per g kidney wt, $P < 0.05$) and additionally to a decrease in the glomerular permeability coefficient, L_pA, from a minimum value of 0.105±0.012 in group 1 to 0.054±0.01 nl/s per g kidney wt per mm Hg ($P < 0.01$) after chronic sodium depletion. There was no difference in fractional proximal tubular reabsorption between group 1 and group 2. Absolute proximal reabsorption (APR) was reduced from 20.8±1.3 in group 1 to 16.3±0.9 […]

Glomerular Hemodynamics in Rats with Chronic Sodium Depletion

EFFECT OF SARALASIN

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ABSTRACT In chronic sodium depletion the glomerular filtration rate may be reduced, and alterations in proximal tubular function may contribute to the maintenance of antinatriuresis. Measurements were made by micropuncture technique in superficial nephrons of the Munich-Wistar rat of (*a*) the determinants of glomerular filtration rate, (*b*) peritubular capillary hydrostatic and oncotic pressure, and (*c*) proximal tubular fractional and absolute reabsorption in both a control group (group 1, $n = 12$) and a group of chronically sodium-depleted rats (group 2, $n = 12$). Single nephron filtration rate (sngfr) was 37.2±1.2 in group 1 and 31.6 ±1.0 nl/min/g kidney wt ($P < 0.05$) in group 2. Of the factors potentially responsible for the observed reduction in sngfr, there was no change in systemic oncotic pressure or the transglomerular hydrostatic pressure gradient. Sngfr was lower in group 2 because of both a reduced single nephron plasma flow (rpf) (128±6 vs. 112±5 nl/min per g kidney wt, $P < 0.05$) and additionally to a decrease in the glomerular permeability coefficient, L_pA, from a minimum value of 0.105±0.012 in group 1 to 0.054±0.01 nl/s per g kidney wt per mm Hg ($P < 0.01$) after chronic sodium depletion. There was no difference in fractional proximal tubular reabsorption between group 1 and group 2. Absolute proximal reabsorption (APR) was reduced from 20.8±1.3 in group 1 to 16.3±0.9 nl/min per g kidney wt in group 2.

The role of angiotensin II (AII) in maintaining glomerular and proximal tubular adaptations to chronic sodium depletion was assessed in subsets of groups 1 and 2 by the infusion of the AII antagonist Saralasin at a rate of 1 μg/kg per min. In group 1 rats, Saralasin had no effect on sngfr, rpf, or L_pA, because animals remained at filtration pressure equilibrium. In group 2 rats, AII blockade was associated with an increase in sngfr from 31.6±1.0 to 37.1±1.7 nl/min per g kidney wt ($P < 0.01$). Rpf increased during Saralasin infusion solely as a result of a decrease in afferent arteriolar resistance from 21.7±2.3 to 15.2±2.3 10^9 dyn-s-cm^{-5} ($P < 0.01$). Saralasin infusion did not affect the reduced L_pA in group 2, as L_pA remained 0.056±0.02 nl/s per g kidney wt per mm Hg and rats remained disequilibrated. In spite of the increase in sngfr in group 2, AII antagonism further decreased APR to 13.1±1.5 ($P < 0.01$). Distal delivery therefore, increased from a control value of 15.3±1.3 to 24.3±1.5 nl/min per g kidney wt ($P < 0.01$).

In conclusion, both a decrease in L_pA and a reduction in rpf were major factors mediating the decrease in glomerular filtration rate observed in chronic sodium depletion. Saralasin infusion revealed a significant effect of AII on rpf and afferent arteriolar resistance in chronic sodium depletion, but no effect of AII on either efferent arteriolar resistance or the decrease in L_pA could be demonstrated. Saralasin had no effect in rats that were not chronically sodium depleted. In group 2 rats AII antagonism reduced APR even though sngfr increased, suggesting an influence of AII on proximal reabsorption. The marked changes observed during Saralasin infusion in the chronically sodium-depleted rat reveal important modifying effects of endogenously generated AII on both the glomerulus and proximal tubule.

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During the tenure of these studies, Dr. Blantz was a Clinical Investigator of the Veterans Administration and Dr. Steiner was a fellow of the Kidney Foundation of Southern California. Mr. Tucker is a doctoral student in Applied Mechanics and Engineering Sciences, University of California, San Diego, Calif. Reprint requests should be addressed to Dr. Blantz, Veterans Administration Hospital, San Diego, Calif. 92161.

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INTRODUCTION

Relatively marked sodium depletion is associated with a depression of the glomerular filtration rate (1). The

determinants of single nephron filtration rate producing this reduction in ultrafiltration and the factors that may influence the rate of proximal reabsorption in this setting have not been examined in detail. Indirect evidence would suggest that in antinatriuretic states such as chronic sodium depletion, angiotensin II (AII) may have important modifying effects upon both the glomerulus and the proximal tubule (2, 3). The purposes of the present study were (*a*) to define the mechanisms whereby nephron filtration rate is reduced in chronic sodium depletion, (*b*) to determine both whether proximal tubular reabsorption is altered in this state and the contribution of peritubular physical factors in sustaining this reabsorption of filtrate, and (*c*) to delineate, by infusion of the AII antagonist, Saralasin, the effects of AII on glomerular and proximal tubular adaptations to chronic sodium depletion.

GLOSSARY OF SYMBOLS

A	Glomerular capillary surface area.
AII	Angiotensin II.
APR	Absolute proximal reabsorption.
AR	Afferent arteriolar resistance.
C_A	Afferent arteriolar protein concentration.
C_E	Efferent capillary blood protein concentration.
DD	Distal delivery.
EFP	Effective filtration pressure.
EFP_A	Afferent effective filtration pressure.
EFP_E	Efferent effective filtration pressure.
ER	Efferent arteriolar resistance.
FPD	Filtration pressure disequilibrium.
FPE	Filtration pressure equilibrium.
FR	Proximal fractional reabsorption.
GFR	Glomerular filtration rate.
HP_E	Mean efferent peritubular permeability.
L_pA	Total glomerular permeability.
MAP	Mean arterial pressure.
P_{BS}	Bowman's space hydrostatic pressure.
P_G	Glomerular capillary hydrostatic pressure.
P_t	Proximal tubular hydrostatic pressure.
ΔP	Hydrostatic pressure gradient across glomerular capillary.
π	Oncotic pressure.
π_A	Systemic oncotic pressure.
π_E	Efferent oncotic pressure.
rbf	Single nephron blood flow.
rpf	Single nephron plasma flow.
snff	Single nephron filtration fraction.
sngfr	Single nephron filtration rate.
TF	Tubular fluid.
$U_{Na}V$	Sodium excretion.
U_KV	Potassium excretion.
x*	Normalized glomerular capillary length.
——	Bar (superscript) designates mean value.

METHODS

Male Munich-Wistar rats weighing 200–250 g were used in the study. Normal control rats (group 1, $n = 12$) were selected the day before micropuncture from our colony, which is maintained with ad lib access to water and normal rat chow (Ralston Purina Co., St. Louis, Mo.), which contains 0.08 meq of Na^+/g. Sodium-depleted rats (group 2, $n = 12$) were injected intraperitoneally with furosemide (1 mg/kg) and fed a sodium-free diet (ICN Nutritional Biochemicals, Cleveland, Ohio) with free access to water for a period of at least 7 d (mean 14.8±3 d). Aside from the sodium contained, the diets used were nearly identical with respect to protein, fat, carbohydrate, and vitamin content. Dietary intake of food was approximately equal in both dietary groups by observation. Immediate weight loss 6–8 h after furosemide injection, while food was withheld, varied from 3–10 g and averaged about 4% body wt. Unexpectedly, the rats continued to lose weight over the first 24 h. This 1st-day loss of body weight averaged 16 g. Weight at micropuncture averaged 99% of initial weight before furosemide. This contrasted with an expected average weight gain of approximately 30 g over the same period in normal rats. After the acute weight loss incurred within the first 24 h, rats on the sodium-free diet gained 16 g before micropuncture compared to the 30 g predicted for normal, undisturbed rats maintained on a normal sodium intake. Both sodium-depleted and normal rats were deprived of food for the 16 h before micropuncture.

In group 1, all determinants of nephron filtration were measured in a control micropuncture period. In 6 of these 12 rats, group 1a, Saralasin (Beckman Instruments Inc., Palo Alto, Calif.) was then infused and a second set of determinants were measured. In the other six rats, group 1b, measurements of proximal tubular fractional and absolute reabsorption were obtained in a single-period study. In group 2, determinants of nephron filtration and measurements of proximal tubular function were evaluated in an initial period in six rats (group 2a) and again after Saralasin infusion. Group 2b ($n = 6$) served as time controls for single nephron filtration rate (sngfr) and measurements of proximal reabsorption. The determinants of nephron filtration were not measured in group 2b; sngfr and tubular reabsorptive rates were measured in two consecutive periods of micropuncture and no Saralasin was given. In summary, sngfr and all of the determinants of glomerular filtration (hydrostatic pressure gradient across glomerular capillary [ΔP], single nephron plasma flow [rpf], total glomerular permeability [L_pA], and systemic oncotic pressure [π_A]) were obtained in groups 1a, 1b, and 2a. Measurements of sngfr and proximal tubular function (fractional reabsorption, absolute proximal reabsorption, and distal delivery) were obtained in groups 1b, 2a, and 2b. Saralasin was infused in groups 1a and 2a.

Animals were prepared for micropuncture as described in several publications from this laboratory (2, 4). All animals received a maintenance infusion of 0.5% body wt/h of an isotonic NaCl-$NaHCO_3$ solution through a jugular vein catheter. Mean arterial pressure (MAP) was monitored through a femoral artery catheter with a Statham p23Db pressure transducer (Statham Instruments, Inc., Oxnard, Calif.). Body temperature was maintained constant by a servo-controlled heated table, activated by a rectal probe. [^{14}C]inulin was infused at a rate of 30–40 μCi/h in the isotonic maintenance infusion. A 1-h equilibration period was allowed before measurements were initiated. The protocol for obtaining basic data at micropuncture has been described (2, 4) and will be briefly outlined. In control and salt-depleted rats, all of the following measurements were obtained. Hydrostatic pressures in the glomerular capillaries (P_G), Bowman's space (P_{BS}), efferent arterioles (HP_E), and surface proximal tubules (P_t) were measured with a glass micropipette 1 μm in external tip diameter, filled with hypertonic saline (1.2 M) in series with a servo-nulling pressure device (Prospective Measurements, Inc., San Diego, Calif.). Coated glass pipettes (1107, Dow Corning Corp., Midland, Mich.) of 13–16 μm o.d. were used to collect efferent (star) capillary blood for determination of protein concentration (C_E). Pipettes containing efferent peritubular

capillary collections were sealed with several applications of Eastman 910 (Eastman Kodak Co., Rochester, N. Y.) and the plasma separated by centrifugation. At least three 7-nl plasma samples were obtained from each collection with a constant volume pipette. Protein concentration was determined by a micro-adaptation of the Lowry protein method (5), as described (2, 4). Each of the three plasma samples were pipetted in triplicate, for a total of nine determinations, which were averaged to a single value for C_E. Afferent arteriolar protein concentration (C_A) was determined in arterial blood from the femoral artery catheter.

Sngfr was determined from the [^{14}C]inulin concentration of plasma samples obtained periodically and the [^{14}C]inulin activity in timed collections from the most distal segments of proximal surface tubules, with a stable mineral oil block of at least 3–4 tubular diameters in length. Late surface segments of proximal tubules were identified by intratubular injection of dilute FD and C dye (Allied Chemical Corp., Specialty Chemicals Div., Morristown, N. J.) contained in a second pipette of 3- to 5-μm external tip diameter. Collections for sngfr and [^{14}C]inulin concentration (tubular fluid) were tipped with mineral oil to prevent evaporation. Total volume of each late proximal collection was determined by transferring the collection to a constant bore glass pipette, which had been precalibrated to determine its individual length-volume relationship. From this data and plasma inulin radioactivity per unit volume (plasma count rate), sngfr, and the ratio of tubular fluid (TF) to plasma inulin activity [$(TF/P)_{IN}$], fractional reabsorption (FR), absolute proximal reabsorption (APR), and distal delivery (DD) were determined for late proximal tubules. FR of filtrate in the late proximal tubule is defined as $1-(P/TF)_{IN}$. APR equals sngfr·(FR), and DD is defined as sngfr-APR.

Urine from the left (micropunctured) and right kidney was collected under oil from a left ureteral catheter and a bladder catheter, respectively, and urine volume flow rate was determined from weight and time of collection. The counts per minute/volume of [^{14}C]inulin in urine and plasma aliquots were then used to calculate kidney glomerular filtration rate (GFR). Urinary sodium and potassium concentrations were determined by flame photometer (Instrumentation Laboratory, Inc., Lexington, Mass.).

When not in use, Saralasin solutions were stored at 4°C and were discarded after 4 wk. The potency of the Saralasin solution used at micropuncture was confirmed periodically by demonstrating its ability to markedly attenuate or abolish the pressor effect of a bolus of AII in separate groups of rats.

FR and proximal tubular function (RF, APR, and DD) were also measured in a separate group of six similarly sodium-depleted rats (time controls, group 2b) during a control period and during a second period in which Saralasin was not infused to evaluate the effects of elapsed time alone on tubular function in the micropuncture preparation.

To assess the effect on sngfr of a reduction in the rate of maintenance infusion, additional two-period studies were performed in 10 salt-depleted rats, which were infused during micropuncture at the lower rate of 0.2–0.3% body wt/h. In 5 of the 10 rats, after control measurements were made, Saralasin was infused at a rate identical to that employed for groups 1a and 2a. The other five rats received only the continuous reduced maintenance infusion and served as time controls.

Calculations. Afferent and efferent oncotic pressures (π_A and π_E) are determined from protein concentrations (C_A and C_E) by the modified equation of Landis and Pappenheimer (6).

$$\pi = 1.76C + 0.28C^2 \text{ (4, 7).}$$

Protein electrophoresis of serum from group 2 rats ($n = 4$) revealed that total protein remained approximately 50% albumin and was therefore not different from control, normal NaCl intake rats (group 1). The transglomerular pressure gradient, ΔP, is calculated as $P_G - P_t$. Afferent effective filtration pressure (EFP_A) is defined as $\Delta P - \pi_A$; efferent effective filtration pressure (EFP_E) is equal to $\Delta P - \pi_E$. Mean effective filtration pressure ($\overline{EFP}$) is determined as:

$$\overline{EFP} = \int_0^1 (\Delta P - \pi)dx^*.$$

Single nephron filtration fraction (snff) is calculated as $1 - C_A/C_E$. Single nephron blood flow (rbf) equals rpf/1 − hematocrit. Afferent arteriolar resistance (AR) equals (MAP $- P_G$)/rbf and is expressed in units of 10^9 dyn-s-cm^{-5}. Efferent arteriolar resistance (ER) is similarly calculated as $(P_G - HP_E)$/rbf − sngfr). Sngfr, rpf, and rbf increase with age and increase in renal mass (7) and are therefore normalized for left kidney mass.

The glomerular permeability coefficient, L_pA (or K_f) is calculated from sngfr, C_A, C_E, rpf, and ΔP by computerized iteration, which derives a unique value for L_pA if $\Delta P \gg \pi_E$. This method of computation has been described in detail (4). If EFP_E equilibrium exists, a unique value for L_pA (K_f) cannot be calculated. However, a minimal value for L_pA (K_f) can be derived for purposes of statistical comparison to the exact values for L_pA (K_f) which can be generated in disequilibrated animals, ($\Delta P \gg \pi_E$). At filtration pressure equilibrium (FPE), the minimum L_pA (K_f) is the lowest value for L_pA (K_f) that satisfies the condition $\Delta P \approx \pi_E$ for a given ΔP, π_A, and rpf.

Statistical analysis. Statistical significance between groups of animals was evaluated by an unpaired t test. When several measurements, e.g., sngfr, were obtained in an individual animal, each of these measurements was entered separately in computing statistical significance, because the number of observations per animal was uniform. Two-way analysis of variance was used to evaluate changes in paired studies (i.e., between control and experimental periods). When only one value for a measurement was obtained per experimental period, e.g., L_pA, a paired t test was employed.

RESULTS

Characteristics of normal and sodium-depleted groups. Group 2 animals in the control condition did not differ significantly from the normal animals in group 1 in MAP, arterial hematocrit or plasma protein concentration (Table I and Table III). Left kidney GFR was lower in the sodium-depleted animals at the time of micropuncture (1.14±0.07 vs. 0.92±0.06 ml/min per g kidney wt, $P < 0.05$). Sodium excretion ($U_{Na}V$) from the left kidney was identical in both groups at the time of micropuncture, as was potassium excretion (U_KV), but urine volume flow was significantly greater in group 1 rats. When excretion from both right and left kidneys were measured $U_{Na}V$ tended to be lower and U_KV higher in group 2.

Determinants of glomerular filtration in normal and sodium-depleted states. Data are presented in Tables II and III. Sngfr in superficial nephrons was higher in both groups 1a and 1b (control state) compared to groups 2a or 2b (e.g., 37.2±1.2 in group 1 vs. 31.6±1.0 nl/min per g kidney wt in group 2a, $P < 0.05$). Thus, the decrease in superficial sngfr after sodium depletion

TABLE I
Comparison of Sodium-Depleted Rats (Group 2) to Normal Controls (Group 1)

	Hematocrit	C_A	GFR	$U_{Na}V$	U_KV	Urine volume
	%	g%	ml/min/g kidney wt	neq/min	neq/min	μl/min/g kidney wt
Group 1 (n = 12)	56±1	5.9±0.1	1.14±0.07	87±16	222±47	1.9±0.1
Group 2 (n = 12)	53±1	5.8±0.1	0.92±0.06	85±11	308±29	1.6±0.1
	NS	NS	$P < 0.05$	NS	NS	$P < 0.05$

(15%) was comparable to the decrease in kidney GFR (19%).

The rpf was moderately but significantly reduced in sodium-depleted, group 2a rats at 112±5 nl/min per g kidney wt when compared to group 1 (control) rats (128±6 nl/min per g kidney wt, $P < 0.01$, Table II). Rbf was also significantly decreased in the sodium-depleted state (288±14 vs. 229±9 nl/min per g kidney wt, $P < 0.05$). C_A and π_A were not increased in group 2a; therefore increased π_A had no role in lowering sngfr. Similarly, there was no difference between groups 1 and 2a with respect to ΔP (34±1 vs. 37±2 mm Hg). The other determinant of sngfr that changed with sodium depletion was L_pA, which decreased from a minimum value of 0.105±0.012 (obtained at filtration pressure equilibrium) to 0.054±0.010 nl/s g kidney wt per mm Hg ($P < 0.05$, Fig. 1, Table II). The decreased L_pA after sodium depletion was also reflected in the higher EFP_E (−1.4±1.0 vs. 4.6±2.1 mm Hg, $P < 0.05$) in group 2a. Thus a decrease in glomerular capillary surface area (A) and(or) local hydraulic permeability (L_p) was a major contributing factor mediating the reduction in sngfr observed with chronic sodium depletion.

Effect of Saralasin on determinants of glomerular filtration in control and sodium-depleted rats. In six group 1 rats (1a, normal NaCl intake) Saralasin was infused after control measurements to determine the effects of this agent in normovolemic animals submitted to the stresses of micropuncture. In group 1a sngfr was 36.8±1.5 in the control condition and 39.3 ±2.1 nl/min per g kidney wt (NS) in the second period during Saralasin infusion (Table III). Similarly, rpf was unchanged at 127±8 and 133±8 nl/min per g kidney wt (NS). As previously stated, FPE occurred in the control condition in rats on normal NaCl intake and this condition persisted during Saralasin infusion (EFP_E was −1.3±1.3 and −1.4±2.5 mm Hg, respectively). Minimum values for L_pA were 0.107±0.017 and 0.123 ±0.030 nl/s per g kidney wt per mm Hg (NS), respectively, before and during Saralasin infusion. MAP did not change significantly after Saralasin in this group (104±2 and 96±6 mm Hg, respectively (NS). P_G, P_t, ΔP,

TABLE II
Determinants of Glomerular Filtration in Normal Controls (Group 1) and Sodium-Depleted Rats (Group 2a)

	Group 1 (n = 12)	Group 2a (n = 6)	
sngfr, *nl/min/g kidney wt*	37.2±1.2	31.6±1.0	$P < 0.01$
rpf, *nl/min/g kidney wt*	128±6	112±5	$P < 0.05$
rbf, *nl/min/g kidney wt*	288±14	229±9	$P < 0.01$
P_G, *mm Hg*	46.8±1.2	49.0±2.1	NS
P_{BS}, *mm Hg*	12.8±0.8	11.8±1.8	NS
ΔP, *mm Hg*	34.0±0.9	37.0±2.0	NS
AR, 10^9 *dyn-s-cm*$^{-5}$	20.1±2.6	21.7±2.3	NS
ER, 10^9 *dyn-s-cm*$^{-5}$	10.7±1.9	14.7±2.0	NS
snff	0.31±0.02	0.29±0.02	NS
π_A, *mm Hg*	20.2±0.7	19.3±0.6	NS
π_E, *mm Hg*	35.2±0.9	32.7±1.4	NS
EFP_A, *mm Hg*	13.8±1.0	17.9±1.7	$P < 0.05$
EFP_E, *mm Hg*	−1.4±1.0	4.6±2.1	$P < 0.05$
L_pA, *nl/s/g kidney wt/ mm Hg*	0.105±0.012*	0.054±0.01	$P < 0.01$

* Minimum possible value for L_pA at FPE.

and π_A were also unchanged by Saralasin infusion in group 1 rats. Therefore, in spite of the acute surgical stresses associated with micropuncture, Saralasin had no effect upon either sngfr or any of the determinants of nephron filtration in rats maintained previously on a normal NaCl intake and not receiving a diuretic.

Saralasin infusion produced a marked reduction in MAP (112±3.4 vs. 93±3.2 mm Hg, $P < 0.01$) in group 2a, sodium-depleted rats (Table III). In spite of this decrease in MAP, there was an increase in sngfr (31.6 ±1.0 vs. 37.1±1.7 nl/min per g kidney wt, $P < 0.01$) with Saralasin. P_G and ΔP did not change. π_A was significantly decreased during Saralasin infusion (19.3 ±0.6 vs. 17.8±0.9 mm Hg, $P < 0.01$); however, the significance of the change in π_A is uncertain because a change in $EFP_A(\Delta P - \pi_A)$ could not be demonstrated. The reduction in L_pA observed after sodium depletion was not reversed by the infusion of Saralasin, as a mean value virtually identical to control was obtained during AII antagonism (0.054±0.01 vs. 0.056±0.02 nl/s per g kidney wt per mm Hg, Fig. 1). The major factor that produced the increase in sngfr during Saralasin infusion was an increase in rpf (112±5 vs. 131±9 nl/min per g kidney wt, $P < 0.01$). This increase in rpf was a result of a decrease in AR (21.7±2.3 vs. 15.2±2.3 10^9 dyn-s-cm^{-5}, $P < 0.01$) alone; ER was unaffected by Saralasin. P_G remained constant, as arterial pressure decreased with the decline in AR. Increases in sngfr and rpf during Saralasin were proportional, thereby maintaining snff constant (0.30±0.02 vs. 0.28±0.02). The sngfr returned to values not different from control, normal NaCl intake, rats (group 1). However, during Saralasin L_pA remained lower than in control rats (group 1) and this effect to decrease sngfr was overcome by the effects of higher values for rpf and lower π_A.

Proximal tubular reabsorption in control and sodium-depleted rats. Although sngfr was reduced in group 2a or 2b compared to group 1b, FR remained constant (0.53±0.04 in both), indicating preservation of glomerulo-tubular balance (Table IV). APR was also significantly reduced in group 2 (e.g. 20.8±1.3 in group 1b vs. 16.3±0.9 nl/min per g kidney wt in group 2a, ($P < 0.02$) and DD was unchanged between groups (17.8±1.1 vs. 15.3±1.3 nl/min per g kidney wt). The reduced APR during sodium depletion occurred despite a lower HP_E (18.5±0.5 vs. 13.9±1.4 mm Hg, $P < 0.01$), and with no change in π_E (35.2±0.9 vs. 32.7 ±1.4 mm Hg, NS).

Influence of Saralasin in proximal tubular function in volume-depleted rats. In Table IV, the effects of Saralasin on proximal tubular function in sodium-depleted rats (group 2a) are compared to the proximal tubular changes occurring in the absence of Saralasin in the sodium-depleted time controls (group 2b). There were no differences between measurements derived in the respective initial periods in groups 2a and 2b (Table IV, rows 2 and 4). $U_{Na}V$ rose after Saralasin infusion but did not change in time controls (group 2b). MAP fell in both groups, but Saralasin infusion was associated with a greater fall in MAP (ΔMAP = 17.7±3 vs. 9.0±3 mm Hg, $P < 0.05$). Sngfr rose in both groups, but the response in proximal tubular function was markedly different in the Saralasin infused group, in that reductions occurred with Saralasin in both FR (0.53±0.04 vs. 0.35±0.05, $P < 0.01$) and APR (16.3±0.9 vs. 13.1±1.5 nl/min per g kidney wt, $P < 0.01$). Neither FR nor APR changed from control in the sodium-depleted animals not infused with Saralasin (group 2b). DD increased in both sodium-depleted groups, but the increase was significantly larger in the Saralasin-infused group (ΔDD = 8.4±1.7 vs. 2.8±0.5 nl/min per g kidney wt, $P < 0.02$), because of the combined effects of both the increase in sngfr and the decrease in APR (Table IV). The decreased APR, mediated by Saralasin infusion, was associated with a fall in π_E and no change in HP_E. DD in the volume-contracted time controls rose significantly with time. Saralasin infusion in group 2a (Table IV) increased DD to values significantly higher than those observed in group 1b (24.3±1.5 vs. 17.8±1.1 nl/min, $P < 0.01$). In the sodium-depleted time controls (group 2b), APR (which did not rise in period 2) remained significantly lower than that measured in normally hydrated controls (14.9±0.8 vs. 20.8±1.3 nl/min, $P < 0.01$).

Because the customary maintenance infusion rate (0.5–0.6% body wt/h) in group 2b (sodium-depleted) rats was associated with an increase in sngfr with time, additional studies were performed at lower maintenance infusion rates (0.2–0.3% body wt/h). In rats not infused with Saralasin ($n = 5$), sngfr remained constant (33.1±1.5 vs. 33.5±1.4 nl/min per g kidney wt, NS). However, during the lower maintenance infusion, Saralasin infusion alone produced a significant increase in sngfr (29.7±1.0 to 37.7±1.6 nl/min per g kidney wt, $P < 0.01$) ($n = 5$), demonstrating further that Saralasin infusion produces an increase in sngfr, independent of any volume or NaCl repletion. When all low-infusion rats were examined by three-way analysis of variance, the single effect of Saralasin upon sngfr was highly significant ($P < 0.001$), and time and maintenance infusion had no effect. Saralasin, therefore, increases sngfr in sodium-depleted rats independent of any sodium and volume repletion produced by maintenance infusion.

Other effects of Saralasin infusion. In group 2a changes in MAP with Saralasin infusion were inversely correlated with changes in kidney GFR ($P < 0.01$), suggesting that both changes were a consequence of AII antagonism. A similar but nonsignificant trend existed at the single nephron level ($P < 0.20$). In Saralasin infused animals, the change in rbf was directly corre-

TABLE III

Effects of Saralasin Infusion on the Determinants of Glomerular Filtration in Normal Controls (Group 1) and Sodium-Depleted Rats (Group 2)

	MAP	sngfr	rpf	rbf	P_G	P_{BS}	ΔP	HP_E
	mm Hg	*nl/min/g kidney wt*	*nl/min/g kidney wt*	*nl/min/g kidney wt*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*
Group 1a (n = 6)								
Control	104±2	36.8±1.5	127±8	292±20	45.7±1.8	11.9±1.0	33.8±1.5	16.6±0.8
Experimental	96±6	39.3±2.1	133±8	298±18	45.8±2.6	14.3±1.3	31.5±1.7	17.5±1.3
	NS	NS	NS	NS	NS	NS	NS	NS
Group 2a (n = 6)								
Control	112±3	31.6±1.0	112±5	229±9	49.0±2.1	11.8±1.8	37.0±2.0	13.9±1.4
Experimental	93±3	37.1±1.7	131±9	265±16	48.4±1.5	13.1±1.1	35.3±1.2	15.3±1.3
	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	NS	NS	NS	NS

* Minimum possible value for L_pA at FPE.

‡ Compared to the respective control condition.

lated with the change in kidney GFR ($P < 0.05$) and inversely correlated with MAP ($P < 0.05$) again suggesting that the changes in all three were a result of AII blockade. There were no significant relationships between $U_{Na}V$ and either MAP or kidney GFR in either group.

DISCUSSION

The present study indicates that a marked decrease in the L_pA and a modest decrease in rpf combine to produce reduction in sngfr in the chronically sodium-depleted rat. As a consequence of the reduction in L_pA, filtration pressure disequilibrium (FPD), defined as $\Delta P \gg \pi_E$, was observed in spite of the decrease in rpf. In chronically normovolemic rats the L_pA is considerably higher and does not participate in the regulation of sngfr in most physiologic states; consequently, FPE has been rather consistently observed under micropuncture conditions similar to those maintained in the present study (group 1). Thus, the reduction in sngfr associated with the relatively common condition of chronic sodium depletion does not appear to be solely mediated by those factors, particularly rpf, which have been demonstrated to be influential in regulating sngfr in chronically normovolemic rats (8, 12). The existence of FPD in chronic sodium depletion also represents a major physiological difference from the FPE normally observed in the chronically normovolemic state (8, 12).

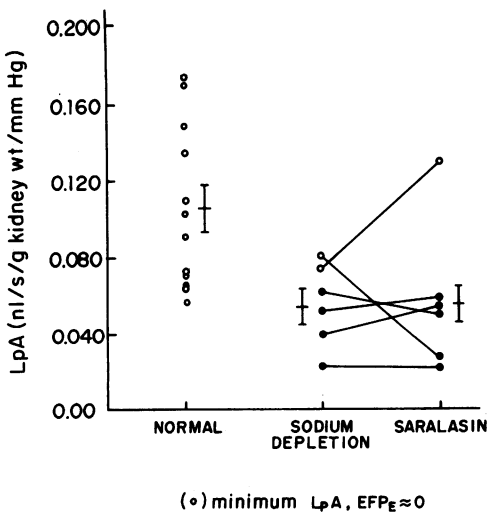

FIGURE 1 The L_pA in chronically normovolemic rats (left), chronically sodium-depleted rats (center), and in the latter group during AII antagonism with Saralasin (right), demonstrating lack of a tonic role of AII in sustaining the reduction in L_pA observed in chronic sodium depletion.

Changes in L_pA have been previously shown to affect sngfr only in certain specific experimental states. As long as FPE occurs, i.e., when $\Delta P \approx \pi_E$, changes in L_pA only affect the point along the glomerular capillary at which filtration ceases, but cannot produce changes in sngfr (8, 9). Because a number of values for L_pA are consistent with a given sngfr at FPE, a specific value for L_pA cannot be calculated at FPE but rather only a minimum possible value. If supranormal values for rpf are produced by plasma volume expansion, FPD occurs, and any change in L_pA will influence sngfr. Conversely, if decreases in L_pA of at least 50% are produced experimentally in the normally hydrated state, e.g., by acute exposure to nephrotoxic substances, or infusion of a variety of hormones (10, 11), FPD may also occur. Only when the condition of FPE is thus prevented by such large decreases in L_pA, may L_pA influence sngfr. Before this study, no data existed to suggest that acute or chronic alterations in volume status may affect L_pA in the rat. In this study, chronic sodium depletion was associated with a sufficiently

AR	ER	snff	π_A	π_E	EFP_A	EFP_E	$\overline{EFP}$	L_pA
10^9 dyn-s-cm^{-5}	*10^9 dyn-s-cm^{-5}*		*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*nl/s/min/g kidney wt/mm Hg*
19.7±3.8	10.0±2.0	0.31±0.03	20.1±1.4	35.1±1.3	13.7±1.5	−1.3±1.3	5.8±1.0	0.107±0.017*
15.8±2.3	10.6±2.4	0.32±0.04	18.3±1.5	32.9±1.6	13.2±1.8	−1.4±2.5	6.1±1.7	0.123±0.030*
NS	NS	NS	NS	NS	NS	NS	NS	NS‡
21.7±2.3	14.7±2.1	0.29±0.02	19.3±0.6	32.7±1.4	17.9±1.7	4.6±2.1	11.0±1.9	0.054±0.01
15.2±2.3	13.9±0.7	0.29±0.02	17.8±0.9	28.7±1.0	18.7±1.7	7.1±1.2	12.9±1.5	0.056±0.01
$P < 0.01$	NS	NS	$P < 0.02$	$P < 0.01$	NS	NS	NS	NS‡

large decrease in L_pA (≅50%) so that FPD resulted in spite of a modest concomitant decrease in rpf. Under these conditions of FPD, the reduction in L_pA contributed significantly to the decrease in sngfr observed during chronic sodium depletion in the rat.

The three other factors that affect sngfr are π_A, ΔP, and rpf. Of these, a change in rpf is the major empirically documented mediator of changes in sngfr in most physiologic states studied to date (9, 12). It was therefore reasonable and predictable to expect that a decrease in rpf should contribute to the reduction in sngfr in chronic sodium depletion. Although ΔP and π_A potentially influence sngfr, no changes in these determinants were demonstrated during modest chronic sodium depletion.

It is possible that the reductions in both rpf and L_pA observed in this study were a result specifically of chronic sodium depletion. Under certain conditions, not entirely similar to those employed in the present study, surgical preparation for micropuncture and the standard rates of NaCl-$NaHCO_3$ maintenance infusion, which helps define the state of "continuous hydropenia," may result in significant acute plasma volume contraction in the rat (13). Such low values for L_pA have not been documented either by us or by Brenner and coworkers (8) when previously normovolemic animals were prepared for micropuncture and maintained in continuous hydropenia in the standard manner (group 1). Thus the reductions in rpf and the glomerular permeability (Lp) and(or) (A) (group 2) may be dependent

TABLE IV

Effects of Saralasin on MAP, Proximal Tubular Function, and Electrolyte Excretion in Normal Control (Group 1) and Sodium-Depleted Rats (Group 2)

	MAP	sngfr	FR	APR	DD	$U_{Na}V$	U_KV	Urine volume
		nl/min/g kidney wt		*nl/min/g kidney wt*	*nl/min/g kidney wt*	*neq/min*	*neq/min*	*μl/min*
Group 1b, $n = 6$	112±2	37.6±1.9	0.53±0.04	20.8±1.3	17.8±1.1	115±24	195±43	1.51±0.13
Group 2								
2a Saralasin infusion; $n = 6$								
Control	112±3	31.6±1.0*	0.53±0.04	16.3±0.9*	15.3±1.3	73±16	275±50	1.39±0.11
Experimental	92±3	37.5±2.0	0.35±0.05	13.1±1.5*	24.3±1.5*	120±17	398±69*	1.68±0.15
	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.02$
2b Time controls, $n = 6$								
Control (1)	117	29.7±2.9*	0.48±0.01	13.8±1.3*	15.9±1.8	98±17	318±37*	1.53±0.13
Control (2)	108	34.1±2.6	0.46±0.02	14.9±0.8	18.7±2.2	108±10	460±108*	1.80±0.14
	$P < 0.05$	$P < 0.02$	NS	NS	$P < 0.01$	NS	NS	$P < 0.01$

* Compared to group 1, $P <$ or $\ll 0.05$.

upon chronic and not acute sodium depletion and may originate as a direct or indirect result of chronic stimuli associated with sodium depletion.

In the condition of FPD produced by the decrease in L_pA after sodium depletion, decreases in rpf also contributed to the decrease in sngfr. Renal plasma flow has also been shown to be reduced after more marked volume contraction than was achieved in group 2 (14). Therefore, with more severe sodium depletion and volume contraction, greater reductions in rpf could obscure the effect on L_pA by maintaining FPE (9). π_A can be elevated by more severe volume contraction (1), and is therefore a potential determinant of sngfr which may also contribute to the larger reductions in filtration rate observed under circumstances of more severe volume contraction.

In the proximal tubule, the reduction in sngfr after chronic sodium depletion was associated with a reduction in APR and an unchanged DD. The finding of unchanged FR and DD in moderately sodium-depleted rats is consistent with previous studies on this issue (1). More severe volume depletion is associated with an increase in FR, and a reduction in DD appears to contribute further to antinatriuresis (1, 15). Peritubular capillary hydrostatic pressure was reduced in the chronically sodium-depleted animals, a finding which should contribute to an increase rather than decrease in APR. Thus, changes in peritubular capillary physical factors could not be demonstrated to mediate the decrease in APR in sodium depletion.

AII is elevated in sodium-depleted rats (16) and could have contributed significantly to alterations in a number of the factors affecting both sngfr and APR. The potential influences of AII upon sngfr have been delineated with infusion studies, demonstrating that AII can decrease rpf, increase P_G, P_t, and ΔP, increase AR and ER, and decrease L_pA and sngfr (2, 3). Because AII may be locally synthesized and degraded in vascular beds, the similarity of AII infusions, even at the most "physiologic" rates, to physiologic conditions observed in stakes of high endogenous AII generation may be questioned. Hence, the influence of ongoing endogenous AII generation may be better delineated by the technique of Saralasin infusion.

In this study, as well as in previous investigations (14), Saralasin infusion in chronic sodium depletion increased renal plasma flow, filtration rate, and sodium excretion, and lowered arterial pressure. However, in group 1a rats, maintained on normal NaCl intake before micropuncture, there was no effect of Saralasin on any of these variables, suggesting a major influence of chronic sodium depletion that is greater than the possible acute effects of micropuncture surgery. Although in some instances Saralasin-mediated reductions in arterial pressure have been observed to abolish the natriuresis (17), this was not the case in the present study in group 2a rats. It is logical to assume that the hemodynamic changes associated with Saralasin infusion after sodium depletion are a consequence of interruption of tonic effects of AII upon the glomerulus. Thus, depending on potentially variable local AII effects, Saralasin infusion could have increased rpf by decreasing either AR or ER, or both. The increase in sngfr could also have been produced by alterations in ΔP. In the present examination, Saralasin decreased AR, which, in spite of the large decrease in MAP, resulted in an increase in both rpf and sngfr, maintaining snff constant. A portion of the decrease in AR observed after Saralasin infusion may have been caused by an autoregulatory response secondary to the Saralasin-induced decrease in MAP ($\cong$50% of the change in AR). However, the fact that rpf increased suggests that there also must have been a Saralasin-specific effect that contributed to this decrease in AR. During the course of these studies, π_A decreased, possibly because of peritoneal protein losses. In group 2a, analysis by a mathematical model of glomerular ultrafiltration revealed that 71% of the increase in sngfr with Saralasin was the result of the increase in rpf and 29% was a consequence of the modest reduction in π_A. These changes in rpf and π_A influenced sngfr by affecting $\overline{EFP}$, which was numerically increased but did not achieve statistical significance because only one value per condition per rat was analyzed (Table III). There were no changes in P_G, P_{BS}, ΔP, ER, and L_pA as a result of Saralasin infusion.

The renal hemodynamic response to the decrease in arterial pressure after Saralasin infusion was unlike that associated with a reduction in perfusion pressure produced solely by mechanical means in chronically normovolemic rats under similar hydropenic micropuncture conditions (18). In the latter situation, decreases in arterial pressure to the level produced in the present study are associated with minimal reductions in sngfr and a reduction in AR, no change in ER, and a decrease in P_G (18). Because Saralasin infusion was associated with an increase in sngfr and in rbf, the reduction in AR cannot be attributed solely to renal autoregulation. Several studies have suggested that exogenous and endogenously generated AII has a primary effect on ER (2, 3, 14, 19). Saralasin infusion demonstrated no tonic effect of AII on ER in chronic sodium depletion in this study, because ER did not change. It remains possible that AII may sustain ER during the autoregulatory response to mechanical reductions in arterial pressure (19), but this hypothesis has not as yet been directly confirmed.

Infusion of AII has been shown to reduce L_pA (2), and the elevated plasma AII found in sodium depletion (16) was a reasonable, potential explanation for the

reduction in L_pA that was demonstrated in sodium depletion (16). However, the same low L_pA persisted during Saralasin infusion. In recent studies (20), we have demonstrated that Saralasin infusion is capable of acutely normalizing the reduction in L_pA produced by acute infusions of AII (2). However it is conceivable that the effects on the glomerular capillary of chronic exposure to AII cannot be reversed acutely by Saralasin, e.g., because of induction of anatomic change by AII (19). It is also possible that either high levels of antidiuretic hormone associated with volume contraction or other regulatory systems, e.g., prostaglandin synthesis (21) and release (22), mediated the reduction in L_pA (10, 11), and that Saralasin infusion does not acutely reverse the effects of such systems. Both of these possible explanations for the inability of Saralasin infusion to correct the reduction in L_pA associated with sodium depletion remain reasonable alternatives.

In the proximal tubule, Saralasin infusion resulted in decreased FR and AR whereas sngfr increased. Glomerulo-tubular balance was thus not maintained during AII blockade, and DD increased to values higher than those observed in rats on a normal NaCl intake (group 1b) under similar micropuncture conditions. These results support the concept that AII somehow maintains and thereby affects APR during chronic sodium depletion. Infused AII has been shown to increase FR and probably to decrease DD (3) in conjunction with an increase in snff, π_E, and a decrease in peritubular capillary blood flow, changes which were proposed to be sufficient to cause the increase in FR (3). In the present study, Saralasin infusion in group 2a produced a small (4 mm Hg) but significant decrease in π_E and a relatively small increase in peritubular capillary plasma flow. Saralasin infusion did not affect HP_E. Although the changes in π_E and peritubular capillary flow were small, it is impossible to exclude the traditional "physical factors" as a cause for the reduction in APR. The direct effects of AII on the proximal tubule are not as yet established. Peritubular capillary perfusion and other studies have produced conflicting results, either suggesting no effect (23), a decrease (24), or an increase (25) in APR mediated by AII. The latter effect may obtain with lower rates of infusion (26). Our results suggest that during sodium depletion, endogenous AII exerts a positive influence by one or more potential mechanisms upon APR. However, it must be emphasized that neither FR nor APR was increased above normal values in the control period in group 2.

Of interest is the finding that sngfr increased over time in sodium depleted rats which were not infused with Saralasin (group 2b, Table IV). It is conceivable that some degree of sodium repletion was achieved by the hydropenic maintenance infusion in the chronically sodium-depleted state. If AII generation were thereby suppressed by sodium repletion, the reduction in AII activity was of lesser magnitude than that achieved with Saralasin infusion, as significant differences in blood pressure, proximal tubular responses, and $U_{Na}V$ were demonstrated between the two groups. Additional studies in sodium-depleted rats that were maintained at lower sustaining infusion rates than group 2b (0.2–0.3% body wt/h) have helped clarify this point. At lower infusion rates sngfr did not change with time. However, even at the lower maintenance infusion rates, Saralasin infusion resulted in a significant increase in sngfr. These additional studies reconfirm the well documented effect of Saralasin to increase sngfr after sodium depletion. These data also suggest that in the sodium-depleted state maintenance infusion rates may result in an increase in sngfr, although the modest volume repletion possibly achieved thereby (in group 2b) was insufficient to increase urinary $U_{Na}V$.

The principal finding of this study was that a decrease in L_pA contributed significantly to the reduction in sngfr associated with chronic sodium depletion. Although changes in rpf have been shown to be the major overall mediator of changes in sngfr in the rat (12), including states with reduced renal perfusion pressure such as aortic constriction in the chronically normovolemic rat (18), a reduction in rpf does not appear to be the only mechanism producing the reduction in sngfr in chronic sodium depletion. In this state, AII appears to maintain, but not increase, afferent arteriolar tone, and to sustain, but not increase, proximal tubular reabsorption. Saralasin infusion studies in normal and sodium-depleted rats suggest a major role for chronic endogenous AII generation in influencing sngfr. The results of the present study also suggest that AII does not directly mediate the reduction in L_pA observed in the chronically sodium-depleted state.

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