On the Mechanism of Inhibition in Fluid Reabsorption by the Renal Proximal Tubule of the Volume-Expanded Rat

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A B S T R A C T We undertook to determine the extent
to which the inhibition in absolute proximal fluid reab-
sorption in response to expansion of extracellular vol-
ume with noncolloid-containing solutions is the result
of concomitant reductions in postglomerular (efferent
arteriolar) protein concentration. Selective elevation of
efferent arteriolar oncotic pressure in volume-expanded
rats (Ringer's 10% body weight) to levels slightly in
excess of normal by microperfusion with 9–10% albu-
min-Ringer's solution nearly completely reversed the
inhibition in absolute and fractional reabsorption in ad-
jacent proximal tubules. In contrast, during similar
microperfusion with a 6–7% albumin solution, no in-
crease in proximal reabsorption was measured. We in-
terpret these findings to indicate that the bulk of the
inhibition in absolute proximal reabsorption in response
to volume expansion with colloid-free solutions is caus-
ally mediated by the accompanying parallel decline in
postglomerular vascular protein concentration.

INTRODUCTION

The nature of the inhibition in absolute fluid reabsorp-
tion that takes place in the renal proximal tubule in
response to acute expansion of extracellular volume has
been the subject of numerous investigations for nearly
a decade (comprehensive reviews and extensive bibli-
ographies may be found in references 1 and 2). The re-
sults of these investigations have led to the identification
of a number of factors as being of potential importance
in mediating this inhibition (1, 2), but because it has
generally not been possible to isolate and separate each
of the seemingly important variables, a rigorous cause
and effect relationship between any single factor and
changes in proximal reabsorption has yet to be provided.

Recently however, this need to reduce the number of
variables has led to the development of a continuous
microperfusion technique for selectively altering the
composition of efferent arteriolar and branch peritubu-
lar capillary blood (3, 4). Indeed this direct approach
has provided us with the opportunity to demonstrate
that the parallel adjustments in proximal fluid reab-
sorption that accompany alterations in glomerular filtra-
tion rate (glomerulotubular balance) are directly re-
lated to, and causally mediated by, the associated changes
in peritubular capillary protein concentration (5). Since
a reduction in postglomerular protein concentration is
among the factors thought important in mediating the
inhibitory response of the proximal tubule to acute ex-
pansion of extracellular volume with noncolloid-con-
taining solutions (6–13), a direct assessment as to
whether a similar cause and effect relationship obtains
under these conditions was undertaken in the present
study. The results indicate that selective restoration of
postglomerular protein concentration to nearly normal
levels in volume-expanded rats (Ringer's 10% body
weight) almost completely reversed the inhibition in
absolute and fractional reabsorption in adjacent proxi-
mal tubules. We conclude therefore that the inhibition
in proximal reabsorption that accompanies volume ex-
pansion with colloid-free solutions is causally mediated
by accompanying reductions in postglomerular vascular
protein concentration.

METHODS

Male Sprague-Dawley rats weighing 284–324 g and allowed
free access to a rat pellet diet and water, were anesthetized
with Inactin (100 mg/kg) and prepared for micropuncture
in a manner described previously (5).

Beginning 60 min before micropuncture each rat received
an intravenous infusion of isotonic saline at the rate of 0.02
ml/min. Inulin was present in a concentration of 10%,
thereby resulting in final plasma concentrations of approxi-

mately 100 mg/ml. Late surface convolutions of proximal tubules were located by observing the passage of Lissamine green dye which was injected rapidly (0.05 ml of a 10% solution) into the right jugular vein catheter. The relative position of each late convolution was mapped so as to facilitate subsequent relocation.

After the 60 min equilibration period, exactly timed (1–2 min) samples of fluid were collected from each experimental tubule for determination of flow rate and inulin concentration, and calculation of single nephron GFR and absolute reabsorptive rate to the site of puncture. The rate of fluid collection was adjusted to maintain a column of polymer oil (Kel F polymer oil; Minnesota Mining & Manufacturing Co., St. Paul, Minn.), three to four tubule diameters in length, in a relatively constant position just distal to the site of puncture. Using the collection technique of controlled suction recently validated for this laboratory (14), we induced minimal changes in tubule diameter and the position of the distal oil block. Sharpened micropipettes with tip diameters of 8–12 μ were employed. Coincident with these tubule fluid collections, femoral arterial blood and three or four timed urine samples were obtained for determination of base line plasma and urine inulin and sodium concentrations and urine flow rate, thereby permitting calculation of inulin clearance and excretion rate of sodium.

Simultaneous estimates of protein concentration in superficial efferent arteriolar and systemic (femoral arterial) blood plasma also were carried out in this study. Methods for selection of vessels for puncture, characteristics and preparation of micropipettes, and techniques of collection and handling of samples, together with the appropriate validating procedural and physiological controls have been described in detail elsewhere (9).

The influence of acute expansion of extracellular volume on these simultaneously measured indices of cortical and whole kidney function then was studied in each rat. After completion of collections in hydropenia, each rat received the intravenous infusion of an isotonic bicarbonate-Ringer's solution (in mmoles/liter: NaCl, 115; KCl, 5; NaHCO₃, 25; Na acetate, 10; NaH₂PO₄, 1.2; MgSO₄, 1.2; CaCl₂, 2.5) at the rate of 0.375 ml/min until a total volume equal to 10% of body weight had been given. Thereafter, the infusion rate was reduced to 0.02 ml/min. Inulin was added to the infusate in quantities calculated to maintain a final plasma concentration of approximately 100 mg/100 ml. Samples of tubule fluid were obtained from previous puncture sites, using controlled suction recollection techniques (14). Separate rather than the same efferent arterioles were punctured after volume expansion. After these control measurements before and during volume expansion, other late proximal tubules were punctured, initially during volume expansion and again during continued volume expansion but now while a neighboring efferent arteriole was selectively perfused with isotonic Ringer's-bicarbonate solution containing either 9–10% or 6–7% crystalline bovine serum albumin.[1] Tubules situated

[1] The Ringer's perfusion solution selected to restore efferent arteriolar protein concentration to nearly normal, preexpansion levels contained crystalline bovine serum albumin in final concentrations of 9–10%. While this provides a total protein concentration equal to that measured at the efferent arteriole in normal hydropenia (5, 8, 9), the effective oncotic pressure of such an albumin solution is slightly higher (by some 10 mmHg) than for an equivalent concentration of a plasma protein solution (5). Thus perfusate solutions are slightly hyperoncotic to native efferent arteriolar plasma. However, during microperfusion some dilution

within the surface zone being perfused with 9–10% albumin comprise the experimental group in which selective restoration of postglomerular vascular protein concentration to control hydropenic levels was accomplished without altering other potential influences on reabsorption induced by volume expansion. The control for this experiment is represented by five tubules in these same rats, which were studied initially during volume expansion, and again while the adjacent efferent arteriole and surrounding branch peritubular capillaries were perfused with isotonic Ringer's-bicarbonate solution containing 6–7 g/100 ml albumin, the concentration which was shown in these same rats to be present in efferent arteriolar blood during volume expansion. Except for the differences in protein concentration, perfusion solutions were identical and contained, in mmoles/liter: NaCl, 110.; NaHCO₃, 25.; Na acetate, 10.; KCl 5.; NaH₂PO₄, 1.2; MgSO₄, 1.2; CaCl₂, 2.5. Final osmolalities, pH, and sodium and potassium concentrations ranged from 261 to 290 mOsm/kg, from 7.38 to 7.42, from 149 to 164, and from 4.1 to 4.8 mEq/liter, respectively. To facilitate accurate delineation of the area being perfused, a blue-green dye (Food Dye and Coloring Green, No. 3; Keystone Aniline & Chemical Co., Chicago, Ill.) was added to each perfusion solution to yield final concentrations of 0.2%. This dye was selected because of its considerably lower sodium concentration than in a similar solution of Lissamine green (approximately 6 mEq/liter for a 0.2% solution). The techniques for microperfusion of efferent arterioles as employed in this laboratory have recently been reported (5).

Analytical. The volume of tubule fluid collected from individual proximal tubules was estimated from the length of the fluid column in a constant bore capillary tube of known internal diameter. The concentration of inulin in tubule fluid was measured, nearly always in duplicate, by the microfluorescence method of Vurek and Pegram (15). Inulin concentrations in urine and plasma were determined by the anthrone method of Führ, Kaczmarczyk, and Krüttgen (16). Sodium concentrations in urine and plasma were determined by flame photometry. Protein concentrations in efferent arteriolar and femoral arterial blood plasmas were determined, usually in duplicate, with an ultramicrocolorimeter (American Instrument Co., Inc., Silver Spring, Md.) using a recently described microadaptation (8) of the technique of Lowry, Rosebrough, Farr, and Randall (17).

Calculations. Single nephron GFR and fractional and absolute reabsorption by the proximal tubule were calculated using standard equations (18).

RESULTS

Mean arterial pressure, C_{In}, and excreted fractions of filtered sodium and water averaged 114 and 110 mmHg, 1.14 and 1.74 ml/min, 0.2 and 2.5%, and 0.1 and 3.6% in hydropenia and volume expansion, respectively. A summary of individual recollection values for TF/P

of the perfusate by native efferent arteriolar blood is observed, thereby tending to minimize any small oncotic differences. Not only would this dilution effect be obtained during hydropenia (a condition during which it has recently been shown that postglomerular microperfusion with an identical 9–10% albumin-Ringer's solution exerts no significant influence on either absolute or fractional proximal reabsorption [5]), but might be expected to be even more pronounced during Ringer's loading when the measured efferent arteriolar protein concentration is reduced to 6–7%.

	Normal hydropenia					Volume expansion—recollections				
				Protein concn.					Protein concn.	
Exp. no.	$\left(\dfrac{TF}{P}\right)_{In}$	SNGFR	Abs. reabs.	EA	FA	$\left(\dfrac{TF}{P}\right)_{In}$	SNGFR	Abs. reabs.	EA	FA
		nl/min	*nl/min*	*g/100 ml*			*nl/min*	*nl/min*	*g/100 ml*	
1	2.06	41.5	21.4	8.7	6.7	1.09	53.0	4.3	6.9	5.2
2	2.90	40.9	26.8	9.2	5.9	1.71	50.6	21.0	6.9	4.5
	2.49	32.6	19.6			1.28	43.3	9.4		
3	2.40	51.0	29.7	9.8	6.7	1.46	69.7	22.0	6.8	5.2
	2.49	48.4	29.0			1.26	48.7	10.0		
4	2.54	52.9	32.1	10.1	6.9	1.64	69.0	27.0	7.1	5.1
	2.68	43.1	27.0			1.88	64.7	30.3		
5	4.29	44.6	34.2	10.2	7.3	1.61	60.0	22.8	7.1	4.7
6	1.94	43.0	20.8	8.5	6.0	1.34	54.1	13.7	6.5	4.9
7	2.98	36.6	24.2	10.0	8.0	1.74	50.5	20.5	7.4	6.0
8	2.28	49.8	27.0	9.7	7.0	1.24	75.4	14.8	7.2	4.8
	2.59	49.3	30.3			1.69	82.6	33.7		
Mean	2.64	44.5	26.8	9.5	6.8	1.49	60.1	19.1	7.0	5.0
± 1 SD	±0.17	±1.8	±1.3	±0.2	±0.2	±0.07	±3.5	±2.6	±0.1	±0.2

Abs. reabs., absolute reabsorption; EA, efferent arteriolar; FA, femoral arteriolar; SNGFR, single nephron glomerular filtration rate.

inulin, single nephron GFR, and absolute proximal reabsorption from 12 tubules is shown in Table I (first and second sections). Data on a given horizontal line are derived from the same tubule studied before and during volume expansion using recollection techniques. Values for simultaneously measured efferent arteriolar and femoral arterial protein concentration are also shown. Expansion of extracellular volume with approximately 30 ml of isotonic Ringer's-bicarbonate solution resulted in a uniform decline in proximal TF/P inulin ratios (mean recollection/initial ratio = 0.58 ±0.03 SE), corresponding to an average fall in fractional reabsorption (from 0.60 ±0.02 SE to 0.31 ±0.03 SE) of 48.6% ±4.8 SE. Single nephron GFR increased in nearly every tubule, the mean change for all recollection pairs of + 35.1% ±4.8 SE not being disproportionately greater than that for the kidney as a whole (mean = + 56.3% ±13.3 SE, n = 4). Absolute proximal reabsorption declined by 15% or more in 10/12 tubules, increased in 2 by 11% and 12%, and fell over-all by an average of 30.3% ±8.0 SE. These changes in nephron

and whole kidney function provide a background against which to examine in a separate set of tubules the influence of selectively restoring postglomerular protein concentration to nearly normal, hydropenic levels (third and fourth sections). Values on a given horizontal line in the third, fourth, and fifth sections of Table I denote initial collections during volume expansion (third section) and recollections performed during efferent arteriolar microperfusion either with 9–10% albumin (fourth section) or 6–7% albumin (fifth section).

Microperfusion of adjacent efferent arterioles and branch peritubular capillaries surrounding 11 of these tubules with an isotonic Ringer's-bicarbonate solution containing 9–10% albumin (a protein concentration equal to that present, on average, in efferent arteriolar blood of these same rats during normal hydropenia [first section]) resulted in a distinct rise in proximal TF/P inulin ratios in all but one nephron (fourth section), the over-all mean recollection/initial ratio averaging 1.41 ±0.08 SE (P < 0.001). The changes in this index of proximal fractional reabsorption were readily

Volume expansion-initial collections			Volume expansion 9–10% albumin microperfusion				Volume expansion 6–7% albumin microperfusion			
$\left(\dfrac{TF}{P}\right)_{In}$	SNGFR	Abs. reabs.	$\left(\dfrac{TF}{P}\right)_{In}$	SNGFR	Abs. reabs.	Perfusion rate	$\left(\dfrac{TF}{P}\right)_{In}$	SNGFR	Abs. reabs.	Perfusion rate
	nl/min	*nl/min*		*nl/min*	*nl/min*	*nl/min*		*nl/min*	*nl/min*	*nl/min*
1.35	60.2	15.6	1.88	76.8	35.9	295.				
1.39	52.6	14.7	1.79	43.8	19.3	295.				
1.06	38.5	2.2	1.64	42.1	16.4	457.				
1.70	72.2	29.7	2.37	50.7	29.3	450.				
1.36	39.1	10.4	1.68	35.7	14.4	540.				
1.47	69.1	22.1	2.42	72.6	42.6	540.				
1.20	75.0	12.6	2.47	80.0	47.6	540.				
1.07	48.5	3.2	1.09	35.6	2.9	540.				
1.24	51.4	10.0	1.66	40.1	16.0	540.				
1.38	45.2	12.4	1.80	47.6	21.2	450.				
1.27	48.0	10.1					1.23	43.9	8.2	450.
1.23	47.4	9.0					1.26	40.6	8.3	294.
1.18	42.9	6.5					1.24	42.9	8.3	294.
1.98	69.1	34.1	2.51	71.7	43.1	294.				
1.87	67.8	31.6					1.86	59.9	27.6	294.
1.15	46.5	6.2					1.14	48.2	5.8	294.
1.37	54.6	14.4	1.94	54.2	26.2		1.35	47.1	11.6	
±0.07	±3.1	±2.5	±0.14	±5.2	±4.3		±0.13	±3.4	±4.0	

apparent despite (*a*) sustained expansion of extracellular volume, (*b*) sustained high, and on average, unchanged values for single nephron GFR (mean change $= -3.7\% \pm 5.7$ SE), (*c*) efferent arteriolar perfusion rates in excess of physiologic flow rates (as estimated from single nephron GFR and single nephron filtration fraction) and therefore despite peritubular capillary hydrostatic pressures likely to be higher than normal,[2] and (*d*) despite a reduction in the viscosity of efferent ar-

[2] In three other rats we measured the effects of efferent arteriolar microperfusion on branch peritubular capillary hydrostatic pressures. Using a servo-nulling transducer (19), pressures were recorded initially during normal blood perfusion and again at the same site in the same capillary during microperfusion of a 9–10% albumin solution. The changes in capillary pressure, which increased in every instance, averaged + 2.6 cm H_2O ±0.2 SE (n = 5), + 3.6 cm H_2O ±0.7 (n = 10), and + 5.9 cm H_2O ±0.8 (n = 9) for perfusion rates of 200, 440, and 680 nl/min, respectively. It is therefore of interest to note that despite the very high flow rates obtained during microperfusion the resulting elevations in peritubular capillary pressure were relatively small.

teriolar fluid in that a cell-free Ringer's-albumin perfusate was substituted for the normally occurring red blood cell-plasma medium. As shown in Table I (fourth section) absolute reabsorption increased by greater than 25% in 10/12 tubules; in 2 this measure remained unchanged from the initial one. For these 12 paired measurements, absolute reabsorption increased an average of 11.1 nl/min ($P < 0.01$). In contrast with this marked enhancement of reabsorption to or toward control hydropenic levels during 9–10% albumin microperfusion, when efferent arterioles adjacent to five other proximal tubules were perfused with 6–7% albumin-Ringer's solution, no significant changes in reabsorption were measured. Thus, paired TF/P inulin recollection ratios averaged 1.00 ±0.01 SE; the resultant mean change in fractional reabsorption was + 1.2% ±8.0 SE. Once again the microperfusion technique was found to exert no systematic influence on simultaneous estimates of single nephron GFR, the paired changes in the latter averaging − 6.2% ±4.4 SE (range: − 14.3 to + 3.6). Consequently absolute reabsorption remained
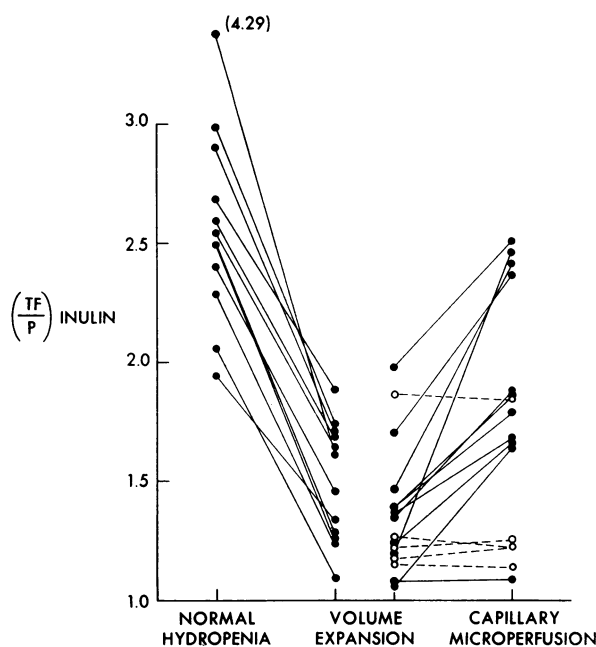
FIGURE 1 Comparison of effects of volume expansion on proximal tubule fluid/plasma inulin ratios in the presence and absence of reductions in postglomerular protein concentration. The solid circles joined by solid lines in the left-hand portion of the figure indicate the changes in TF/P inulin ratios induced by volume expansion in 12 proximal tubules. The solid lines in the right-hand portion of the figure join TF/P inulin values from 11 other proximal tubules (solid circles) studied initially during volume expansion and again during continuous microperfusion of an adjacent efferent arteriole and its branch peritubular capillaries with a Ringer's-bicarbonate solution containing 9–10 g/100 ml crystalline bovine serum albumin. The microperfusion control is indicated by five tubules (open circles and dashed lines) studied initially during volume expansion, and again during efferent arteriolar microperfusion with Ringer's-bicarbonate containing 6–7 g/100 ml albumin. The recollection micropuncture technique was employed throughout.

unchanged (over-all mean = − 3.6% ±8.2 SE, [P > 0.2]). The range of efferent arteriolar microperfusion rates for these five experimental tubules (fifth section) was similar to that for the group receiving 9–10% albumin-Ringer's solution (fourth section). In this regard, absolute reabsorption rose in the three nephrons perfused with 9–10% albumin at rates of 295 nl/min and failed to rise in the four nephrons perfused with 6–7% albumin at 294 nl/min. Absolute reabsorption failed to rise in the single nephron perfused with 6–7% albumin at 450 nl/min and rose in 6/8 nephrons perfused with 9–10% albumin at 450–540 nl/min. Furthermore, in a recent capillary microperfusion study (5) neither absolute nor fractional proximal reabsorption was found to be systematically influenced by capillary perfusion rate per se, in that during 9–10% albumin microperfu-

sion, reabsorption remained constant at perfusion rates ranging from 260 to 590 nl/min. We conclude therefore that the increase in reabsorption observed in the present study during 9–10% albumin perfusion was not the consequence of an influence of perfusion rate per se.

A summary of the individually paired proximal TF/P inulin ratios achieved in this group of eight rats is given in Fig. 1.

DISCUSSION

Despite the long-standing and intensive interest of a number of investigators, there is to date no evidence of a causal nature to account for the fall in absolute proximal fluid reabsorption that accompanies expansion of extracellular volume with colloid-free solutions (1, 2). The formidable nature of the evidence indicating that proximal sodium reabsorption is an active, energy-requiring process led workers to propose that the natriuretic response to volume expansion was likely to be the consequence either of a circulating inhibitor of tubule reabsorption (20–22) or of influences exerted at the luminal boundaries of renal epithelial cells ultimately to reduce the availability of sodium for active transport (23–27). The demonstration by Vogel, Heym, and Andersohn (28) in 1955 that sodium reabsorption in the amphibian kidney could be enhanced by increasing the oncotic pressure within peritubular capillaries remained little more than a curious observation, much like the earlier proposals of Ludwig (29) and the then current evidence of Bresler (30), largely because of the prevailing belief that such passive physical factors were unlikely determinants of these reabsorptive processes. The more recent studies of Earley, Nizet, Vereerstraeten, and their respective co-workers (6, 10–13, 31–34) in the dog and avian kidney nevertheless have provided increasingly more rigorous experimental evidence to support the notion that a direct relationship might account for the observed parallel changes in rates of tubule sodium reabsorption (under a variety of experimental conditions) and the simultaneous balance of Starling forces operating across peritubular capillaries. Such findings led Earley and his co-workers (6, 31–33) to propose that changes in the net balance of oncotic and hydrostatic forces operating at the level of the peritubular capillary wall serve to influence rates of uptake and removal of the epithelial reabsorbate by the peritubular microcirculation. Additional support for such a notion was provided by the recent demonstration by Lewy and Windhager (7) that in the normal rat a direct and roughly linear relationship obtained between filtration fraction and the rate of proximal sodium reabsorption, a conclusion recently verified by more direct measurements by Brenner and co-workers (8, 9). In an effort to link these purely passive physical forces de-

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termining the rate of removal of tubule reabsorbate with the already well established active mode of isotonic sodium transport, Lewy and Windhager (7) emphasized that the lateral intercellular channels situated between adjacent epithelial cells might function in a manner analogous to that of the middle compartment of Curran and MacIntosh (35). Given the assumption that active transport sites for sodium are located along the walls of these channels primarily at their luminal margins, it becomes theoretically possible to establish a localized standing osmotic gradient (36), and thereby provide the basis of an integrated mechanism in which passive Starling forces might ultimately regulate the net transfer of sodium chloride and water from lumen to peritubular capillary blood.

The simultaneous and independent development of a continuous microperfusion technique for selectively altering the composition of efferent arteriolar and branch peritubular capillary blood by Spitzer and Windhager (3) and Rumrich and Ullrich (4) has afforded the opportunity to examine in direct fashion the influence of changes in peritubular capillary oncotic forces on reabsorption in adjacent proximal tubules independent of the heretofore troublesome and confusing concomitant alterations in renal hemodynamics. With this approach a direct and causal relationship has been demonstrated between postglomerular oncotic pressure and proximal fluid reabsorption in the rat under conditions in which dextran (3) and crystalline bovine serum albumin (5) provided the oncotic force.

Accordingly the present study was undertaken in an effort to characterize by similarly direct methods the extent to which the inhibition in absolute proximal reabsorption that takes place in response to acute expansion of extracellular volume with noncolloid-containing solutions is the consequence of the expected (as well as measured) fall in postglomerular (efferent arteriolar) protein concentration. Cortical efferent arteriolar protein concentration declined on average by 27% during Ringer's loading. Microperfusion of surface efferent arterioles and their branch peritubular capillaries with an artificial plasma having a protein concentration similar to that measured after volume expansion (6–7 g/100 ml) did not alter the effects of volume expansion on several measures of nephron function including estimates of proximal absolute and fractional reabsorption, tubule fluid flow rate, or calculated values for single nephron GFR. Selective restoration of the efferent arteriolar protein concentration in volume-expanded rats to nearly normal levels by microperfusion with 9–10% albumin-Ringer's resulted in a nearly uniform reversal of inhibition in absolute and fractional reabsorption in adjacent proximal tubules. Restoration of reabsorption on average to within 80% of control was demonstrable

despite continued high and over-all unchanged rates of glomerular filtration, and despite marked and sustained expansion of extracellular volume. Moreover both viscosity and hydrostatic pressure were altered in directions that would be expected to inhibit further rather than to enhance reabsorption. Finally, since during microperfusion, extracellular volume remained expanded, the restoration of proximal reabsorption toward control values by 9–10% albumin-Ringer's makes unlikely the possibility that a circulating humoral inhibitor is the predominant factor mediating the depression of reabsorption by this segment. These findings therefore provide evidence of a causal nature to indicate that inhibition of proximal sodium reabsorption in response to acute expansion of extracellular volume is in large part mediated by the accompanying changes in postglomerular vascular protein concentration. This conclusion together with the recent evidence from this laboratory (5) that the glomerulotubular balance of salt and water by the proximal tubule is likewise causally mediated by changes in postglomerular vascular protein concentration (induced by intrarenal hemodynamic adjustments leading to alterations in filtration fraction) lends credence to the view that these exaggerated and seemingly unrelated experimental conditions are, as recently discussed (5), interrelated, albeit special, aspects of the more general and fundamental phenomenon of the intrarenal control of sodium excretion.

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