Control of Proximal Tubule Fluid Reabsorption in Experimental Glomerulonephritis

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ABSTRACT We have recently shown that in the early autologous phase of nephrotoxic serum nephritis (NSN) single nephron glomerular filtration rate is unchanged from values in normal hydropenic control rats, but that single nephron filtration fraction and efferent arteriolar oncotic pressure (π_E) are reduced because of a marked reduction in the glomerular capillary ultrafiltration coefficient. The present study was undertaken to examine the influence of this decline in π_E as well as the other known determinants of peritubular capillary fluid exchange on absolute proximal fluid reabsorption (APR) in NSN. The findings indicate that APR and proximal fractional reabsorption are reduced significantly in NSN, relative to values in a separate group of age and weight-matched normal hydropenic control rats studied concurrently. In addition to the measured decline in π_E, efferent arteriolar plasma flow (Q_E) and peritubular capillary hydraulic pressure (P_C) were found to increase significantly, while interstitial oncotic pressure, estimated from hilar lymph, was not significantly different from values in control rats. Using a mathematical model of peritubular capillary fluid uptake we found that, assuming that the capillary permeability-surface area product and interstitial hydraulic

pressure are unchanged in NSN, the observed changes in π_E and P_C are sufficient to offset the effect of the increase in Q_E, yielding a calculated reduction in APR of ~ 4 nl/min, in excellent agreement with the observed mean decline of 4.1 nl/min. These findings suggest that control of APR in NSN is mediated by the same factors that regulate APR under normal physiological conditions, namely, the imbalance of forces governing peritubular capillary uptake of isotonic reabsorbate.

INTRODUCTION

Recent investigations in several laboratories (1–4) using an experimental model of acute, proliferative glomerulonephritis in the rat have focused attention on the coupling between single nephron glomerular filtration rate (SNGFR)[1] and the absolute rate of fluid reab-

[1] *Abbreviations used in this paper:* A/G, albumin/globulin; AP, femoral arterial pressure; APR, absolute rate of fluid reabsorption by the renal proximal tubule; C, protein concentration; C_A, C_E, afferent and efferent C, respectively; C_L, hilar lymph protein concentration; FF, filtration fraction; GBM, glomerular basement membrane; K_f, ultrafiltration coefficient; K_r, reabsorption coefficient; NSN, nephrotoxic serum nephritis; ΔP, transcapillary hydraulic pressure difference; P_C, P_E, P_{GC}, P_T, hydraulic pressure in peritubular capillaries, efferent arterioles, glomerular capillaries, and proximal tubules, respectively; P_r, net driving force of reabsorption; P_{UF}, driving pressure for ultrafiltration; P_{UF_A}, P_{UF_E}, net P_{UF} at the afferent and efferent ends, respectively, of the glomerular capillary; π, colloid osmotic pressure; $\Delta\pi$, transcapillary osmotic pressure difference; π_A, π_E, π_i, π_T, afferent arteriole, efferent arteriole, interstitial, and proximal tubule π, respectively; Q_A, Q_E, afferent and efferent arteriolar plasma flow, respectively; SNFF, single nephron filtration fraction; SNGFR, single nephron glomerular filtration rate; $(TF/P)_{In}$, tubule fluid-to-plasma inulin concentration ratio; V_{TF}, tubule fluid flow rate; — (over a symbol), mean value.

sorption by the renal proximal tubule (APR) in this disorder. In each study it was observed that as filtration rate was reduced, the absolute rate of fluid reabsorption to the end of the proximal convoluted tubule was likewise reduced, although not always in proportion to the reduction in SNGFR. The precise mechanism by which such coupling of glomerulus-proximal tubule function takes place in this glomerulopathy is not readily apparent from the available data.

Extensive evidence exists to indicate that in the normal animal the regulation of APR is controlled to an important extent by changes in efferent arteriolar oncotic pressure (π_E) (5–14). We have recently reported that in the early autologous phase of nephrotoxic serum nephritis (NSN) single nephron filtration fraction (SNFF) and hence π_E were reduced below normal because of a marked reduction in the glomerular capillary ultrafiltration coefficient (K_f). The present study was undertaken in the rat to examine the extent to which alterations in the peritubular capillary driving forces for fluid absorption account for the changes in APR shown to occur in this model of experimental glomerulonephritis.

METHODS

Induction of experimental glomerulonephritis. NSN was induced in 17 adult Munich-Wistar rats in the manner described recently (15). Briefly, after 24-h urine collections for protein determination, the rats were preimmunized by footpad injection with 0.5–1.0 mg of partially aggregated rabbit immune gamma globulin (IgG) in complete Freund's adjuvant. 48 h later a small dose of rabbit anti-rat glomerular basement membrane (GBM) antiserum (containing 41 μg of kidney-fixing antibody in 0.25 ml) was injected into the tail vein. 24-h urine collections for protein determination were begun immediately after injection of the antiserum and at various times thereafter until the day of micropuncture. The determinants of glomerular ultrafiltration and proximal tubule fluid reabsorption were measured by appropriate micropuncture techniques 5–16 days after injection of nephrotoxic serum.

After micropuncture measurements sections of each kidney were prepared for histologic examination utilizing light, electron, and immunofluorescence techniques as described previously (15).

Clearance and micropuncture studies. Experiments were performed in 35 adult mutant Wistar rats weighing 174–336 g and allowed free access to water but not food for 24 h before study. Rats were anesthetized with Inactin (100 mg/kg) and prepared for micropuncture as described previously (10, 14, 16). 60 min before micropuncture rats received an intravenous infusion of isotonic NaCl at the rate of 0.02 ml/min. Inulin was present in a concentration of 10%, thereby resulting in final plasma concentration of about 100 mg/100 ml. Mean femoral arterial pressure ($\overline{AP}$) was monitored by means of an electronic transducer (model P23Db, Statham Instruments, Inc., Oxnard, Calif.) connected to a direct-writing recorder (model 7702B, Hewlett-Packard Co., Palo Alto, Calif.). After this 60-min equilibration period, exactly timed (1–2-min) samples of fluid were collected from the last surface convolution of each

experimental tubule for determination of flow rate and inulin concentration, and calculation of SNGFR and APR. Late proximal convolutions were located either by intravenous injection of Lissamine green dye (0.05 ml of a 5% solution) or by injection of a small oil droplet and observation of its movement along the tubule. The rate of fluid collection was adjusted to maintain a column of polymer oil (Kel F polymer oil, 3M Co., Medical Products Division, St. Paul, Minn.), 3–4 tubule diameters in length, in a relatively constant position just distal to the site of puncture. By using the collection technique of controlled suction previously validated for this laboratory (17), minimal changes in tubule diameter or the position of the distal oil block were produced. Coincident with these tubule fluid collections, femoral arterial blood samples were obtained for determinations of hematocrit and plasma inulin concentration.

Microvascular and nephron hydraulic pressures were measured with a continuous recording, servo-nulling micropipette transducer (16, 18, 19). Micropipettes with outer tip diameters of 2–3 μm and containing 2.0 M NaCl were used. Hydraulic output from the servo system was channeled via an electronic transducer (model P23Db, Statham Instruments, Inc.) to a second channel of the recorder. Accuracy, frequency response, and stability features of this servo system have been reported previously (16). Direct measurements of mean hydraulic pressure in single glomerular capillaries ($\overline{P}_{GC}$), proximal tubules (P_T), efferent arterioles (P_E), and second- or third-order peritubular capillaries (P_C) were recorded in each rat.

To obtain estimates of colloid osmotic pressure (π) of plasma entering and leaving glomerular capillaries and to determine SNFF (see Eq. 6), protein concentration (C) in femoral arterial and efferent arteriolar blood plasmas were measured as described previously (20–23). π calculated for femoral arterial plasma is taken as representative of π for the afferent arteriole (π_A). π for control rats was calculated from these measured values of C by using the equation:

$$\pi = 1.63C + 0.294C^2 \tag{1}$$

where C is expressed in g/100 ml. This equation has been shown by us (24) to agree to within 1% of the more commonly employed empirical equation derived by Landis and Pappenheimer (25). Eq. 1 assumes an albumin/globulin (A/G) ratio of 1.0, the ratio found in normal hydropenic rats in this laboratory (Table IV). For plasma from 14 of the nephritic rats examined, the A/G ratio usually was found to be less than 1.0, averaging 0.76±0.04 SE. It was previously determined in this laboratory, however, that for NSN rats with this A/G ratio, values of π for protein concentrations over the range of 4–10 g/100 ml were not significantly different from values calculated by using Eq. 1 (15). As reported previously (15), for NSN rats with an A/G ratio of 0.4, values of π for protein concentrations over the range of 4–10 g/100 ml are described by the equation:

$$\pi = 2.24C + 0.180C^2 \tag{2}$$

Accordingly, for rats in the present study with A/G ratios between 0.4 and 0.8, the coefficients were determined by linear interpolation of the coefficients in Eqs. 1 and 2.

In addition to these measurements of femoral arterial and efferent arteriolar plasma protein concentrations, protein concentration and A/G ratios were determined on samples of hilar lymph to obtain estimates of interstitial colloid osmotic

pressure (π_l).[2] Since for hilar lymph samples the A/G ratio was always in excess of 1.0 (Table IV), oncotic pressure was determined by linear interpolation between the values calculated from the equations given by Landis and Pappenheimer for plasma and for pure albumin solutions (25). Little uncertainty is involved in this interpolation since at the low concentrations involved oncotic pressure calculated from the two equations differs by no more than 1 mm Hg.

Analytical. The volume of tubule fluid collected from individual nephrons 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, usually in duplicate, by the microfluorescence method of Vurek and Pegram (29). Inulin concentration in plasma was determined by the macroanthrone method of Führ, Kaczmarczyk, and Krüttgen (30). Protein concentrations in efferent arteriolar and femoral arterial blood plasmas and in renal hilar lymph were determined, usually in duplicate, with an ultramicrocolorimeter[3] using a previously described (8) microadaptation of the method of Lowry, Rosebrough, Farr, and Randall (31).

Calculations. Single nephron glomerular filtration rate:

$$\mathrm{SNGFR} = (\mathrm{TF/P})_{\mathrm{In}} \cdot V_{\mathrm{TF}} \qquad (3)$$

where $(\mathrm{TF/P})_{\mathrm{In}}$ and V_{TF} refer to tubule fluid-to-plasma inulin concentration ratio and tubule fluid flow rate, respectively.

Fractional reabsorption:

$$\text{Fractional reabsorption} = 1 - (\mathrm{P/TF})_{\mathrm{In}} \qquad (4)$$

Absolute proximal reabsorption:

$$\mathrm{APR} = \mathrm{SNGFR} - V_{\mathrm{TF}} \qquad (5)$$

Single nephron filtration fraction:

$$\mathrm{SNFF} = 1 - \frac{C_A}{C_E} \qquad (6)$$

where C_A and C_E denote afferent and efferent arteriolar protein concentrations, respectively.

Initial glomerular plasma flow rate (Q_A):

$$Q_A = \frac{\mathrm{SNGFR}}{\mathrm{SNFF}} \qquad (7)$$

Efferent arteriolar plasma flow rate (Q_E):

$$Q_E = Q_A - \mathrm{SNGFR} \qquad (8)$$

An estimate of the net ultrafiltration pressure at the afferent end of the glomerular capillary $(\mathrm{P_{UF_A}})$ is given by the expression:

$$\mathrm{P_{UF_A}} = \bar{\mathrm{P}}_{\mathrm{GC}} - \mathrm{P_T} - \pi_A \qquad (9)$$

An estimate of the net ultrafiltration pressure at the efferent end of the glomerular capillary $(\mathrm{P_{UF_E}})$ is given by

the equation:

$$\mathrm{P_{UF_E}} = \bar{\mathrm{P}}_{\mathrm{GC}} - \mathrm{P_T} - \pi_E \qquad (10)$$

Eqs. 9 and 10 contain the assumption that the colloid osmotic pressure of fluid in Bowman's space (π_T) is negligible. This assumption has been validated by the finding in three NSN rats with relatively heavy proteinuria that the protein concentration in Bowman's space remains less than 200 mg/100 ml. Accordingly, π_T is well below 1 mm Hg.

Mean glomerular transcapillary hydraulic pressure difference:

$$\Delta \bar{\mathrm{P}} = \bar{\mathrm{P}}_{\mathrm{GC}} - \mathrm{P_T} \qquad (11)$$

The glomerular capillary ultrafiltration coefficient (K_f) is calculated by using a differential equation which gives the rate of change of C with distance along an idealized glomerular capillary. This equation, together with its derivation and the method for its solution, is described elsewhere (32). The coefficient for reabsorption of fluid along peritubular capillaries (K_r) is estimated in a similar manner by using equations reported in detail elsewhere (28).

RESULTS

General. Rats with NSN appeared healthy. Edema formation was not detected. The kidneys were of normal size and color, and all tubules, vessels, and glomeruli appeared normal at the time of micropuncture.

Histopathology. As noted in a previous study (15), lesions were confined almost exclusively to the glomerular capillaries, all of which underwent segmental proliferation of mesangial and endothelial cells with resultant obliteration of some capillary lumina. Endothelial cells appeared normal, although in some areas the endothelium was absent and replaced by polymorphonuclear leukocytes. Tubule morphology was found to be normal.

By immunofluorescence microscopy rabbit IgG, rat IgG, and rat C3 component of complement were observed in a uniform linear distribution in the capillary walls of all glomeruli examined. Renal tubule cells, tubule basement membranes, and nonglomerular vascular structures did not stain with these immunofluorescence reagents except for scattered, interrupted linear deposits of C3 component of complement in tubule basement membranes, also seen in control rats.

Proteinuria. Before injection of nephrotoxic serum mean 24-h protein excretion was 16 ± 2 mg $(n = 15)$ in NSN rats, similar to the value of 11 ± 2 mg $(n = 13)$ in control rats $(P > 0.1)$. Protein excretion averaged 20 ± 5 mg $(n = 16)$ in the 24-h period following injection of nephrotoxic serum and 26 ± 15 mg $(n = 13)$ at 4 days after injection. The 24-h urine collections just before micropuncture revealed that most, but not all, rats developed proteinuria, averaging 30 ± 7 mg/24 h $(n = 6)$ $(P < 0.05$ compared to preinjection values).

Whole kidney and single nephron function in NSN vs. control rats. Table I summarizes the mean values for several indices of whole animal and whole kidney

TABLE I
Whole Kidney Function in Control and Experimental Rats

	Body wt	Kidney wt	GFR	AP	Femoral arterial		24-h urine collections	
					Hct	C	$U_{Na}V$	U_KV
	g		ml/min·g kidney wt	mm Hg	vol %	g/100 ml	μeq/min·kidney	
Control	270	0.95	0.96	113	0.51	5.1	0.18	0.38
	±8	±0.03	±0.07	±2	±0.01	±0.1	±0.02	±0.04
	(18)	(18)	(7)	(18)	(18)	(18)	(12)	(12)
NSN	231	0.96	0.89	118	0.50	5.1	0.13	0.46
	±10	±0.05	±0.03	±3	±0.01	±0.1	±0.02	±0.07
	(17)	(16)	(15)	(17)	(17)	(17)	(12)	(12)
P value*	<0.025	>0.5	>0.2	>0.1	>0.2	>0.5	>0.1	>0.2

Values are expressed as means±1 SE. The number of rats studied is given in parentheses. Hct, hematocrit; $U_{Na}V$, U_KV, absolute sodium and potassium excretion rates, respectively.
* Significance of differences in means between control and experimental rats determined from unpaired data by Student's *t* test.

function during hydropenia in control and NSN animals. The animals were of similar body weight and exhibited no significant differences in mean kidney weights, whole kidney GFR, or femoral arterial blood pressure, hematocrit, or protein concentration between groups. Mean 24-h urinary sodium and potassium excretion rates, measured in the 24-h period before micropuncture, were not significantly different between groups.

The measured determinants of glomerular ultrafiltration in control and NSN rats are summarized in Table II. As with whole kidney GFR, mean values for SNGFR were not significantly different between groups, averaging 27.7 nl/min in NSN and 29.1 nl/min in control rats. The coefficient of variation[4] in SNGFR was nearly the same in NSN rats as for the control group, averaging 19.9±3.3% vs. 15.5±2.3% (P > 0.2), respectively, thereby indicating continued homogeneity of function among individual nephrons in NSN rats. Average values for SNFF were significantly lower in NSN rats (0.30±0.02) than in the control group (0.37± 0.01, P < 0.005). Q_A, on average, was higher in NSN rats (97.7±8.5 nl/min) than in controls (80.1±6.0 nl/ min), although this difference was not significant statistically (P > 0.1). SNFF was lower in NSN animals than controls despite the fact that $\bar{P}_{GC}$ and the mean transcapillary hydraulic pressure difference ($\overline{\Delta P}$) were significantly higher in NSN than in control rats. P_T remained unchanged from control values in NSN rats, averaging 11.4±0.2 mm Hg and 10.7±0.3 mm Hg, re-

[4] Coefficients of variation were calculated as the ratio of the standard deviation to the mean value of SNGFR and expressed as a percentage. This calculation was performed in all rats in which three or more values of SNGFR were obtained.

spectively (P > 0.1). The finding that the coefficient of variation of P_T among different nephrons averaged 5.1±0.9% in NSN rats compared to 4.5±1.9% in controls (P > 0.5) provides a further measure of the homogeneity of function among nephrons in NSN animals.

From the measured values of C_A and C_E, values for π_A and π_E were calculated for control and NSN rats (Table II). As given in Eqs. 9 and 10, the magnitude of the glomerular transcapillary pressure differences favoring ultrafiltration at afferent (P_{UF_A}) and efferent (P_{UF_E}) ends of the capillary network were determined for each rat. In control rats, P_{UF_A} averaged 16.9±0.8 mm Hg. The imbalance of pressures favoring filtration disappeared by the efferent end of the glomerular capillaries, P_{UF_E} averaging − 0.1±0.6 mm Hg, thereby denoting achievement of filtration pressure equilibrium. P_{UF_A} was significantly higher (P < 0.001) in NSN rats than in controls, averaging 25.7±1.6 mm Hg. A significant force for ultrafiltration existed all along the glomerular capillaries in NSN animals, P_{UF_E} averaging 14.8±2.3 mm Hg, thus indicating that filtration pressure equilibrium did not obtain in these animals.

If filtration pressure equilibrium is not achieved, i.e. when $\pi_E/\overline{\Delta P} < 1$, a unique value of the glomerular capillary ultrafiltration coefficient, K_f, can be calculated (23, 32). In 11 of the 12 NSN rats in which all of the determinants of glomerular ultrafiltration were measured, equilibrium did not obtain. K_f for these animals averaged 0.026±0.004 nl/(s·mm Hg), a value similar to that reported previously by us for NSN rats (15) and approximately one-third that found in the normal rat (23).

The mean driving pressure for ultrafiltration, $\bar{P}_{UF}$,

TABLE II

Summary of the Measured Determinants of Glomerular Ultrafiltration in Control and Experimental Animals

	$\bar{P}_{GC}$	$\overline{\Delta P}$	π_A	π_E	P_{UF_A}	P_{UF_E}	$\pi_E/\overline{\Delta P}$	SNGFR	SNFF	Q_A
	mm Hg		mm Hg		mm Hg			nl/min		nl/min
Control	43.6	32.9	16.2	32.8	16.9	−0.1	1.01	29.1	0.37	80.1
	±0.7	±0.8	±0.3	±0.8	±0.8	±0.6	±0.02	±1.8	±0.01	±6.0
	(16)	(16)	(18)	(18)	(16)	(16)	(16)	(18)	(18)	(18)
Glomerulonephritis	52.8	41.3	16.2	27.3	25.7	14.8	0.66	27.7	0.30	97.7
	±1.2	±1.4	±0.5	±1.1	±1.6	±2.3	±0.05	±2.0	±0.02	±8.5
	(12)	(12)	(17)	(17)	(12)	(12)	(12)	(17)	(17)	(17)
P value*	<0.001	<0.001	>0.5	<0.001	<0.001	<0.001	<0.001	>0.5	<0.005	>0.1

Values are expressed as means ±1 SE. The number of rats studied is given in parentheses.
* As defined for Table I.

was calculated from the equation:

$$\bar{P}_{UF} = \frac{SNGFR}{K_f} \quad (12)$$

Accordingly, $\bar{P}_{UF}$ averaged 17.8 mm Hg in NSN compared with a maximum value of 6.2 mm Hg estimated for the control group where K_f was assumed to be 0.078 nl/(s·mm Hg), the latter value previously determined in this laboratory for the normal rat (23). The pressures and flows governing glomerular ultrafiltration as summarized in Table II are very nearly the same as those reported previously by us for a similar group of control and NSN rats (15).

The measured determinants of proximal tubule fluid reabsorption in control and NSN rats are summarized in Table III. Although no significant differences were noted between groups for mean values of P_T or P_E, there was a small rise in P_C in NSN rats (9.9±0.4 mm Hg) relative to controls (8.0±0.4 mm Hg, $P < 0.005$). As a consequence of the lower SNFF in NSN rats (Table II), C_E and hence π_E were significantly lower than in control rats. Q_E however, was significantly higher in NSN than control rats, averaging 74.2±7.5 and 52.1± 4.8 nl/min, respectively ($P < 0.025$). Although SNGFR remained unchanged in NSN from control values, APR and therefore proximal fractional reabsorption were reduced significantly in NSN rats. APR averaged 14.3± 0.8 nl/min in control compared with 10.2±1.1 nl/min in NSN ($P < 0.005$), corresponding to a mean difference of 29%. End-proximal (TF/P)$_{in}$ ratios averaged 2.06±0.07 in control vs. 1.64±0.06 in NSN rats ($P < 0.001$). Thus, proximal fractional reabsorption averaged 50.5±1.7% in control and 37.5±2.7% in NSN rats.

Fig. 1 shows values of APR plotted as a function of SNGFR for each control (open circles) and experimental (closed circles) rat. Each point represents the average of values obtained from 2–5 individual tubules. The solid regression line, calculated by the method of least squares, is given for control data by the equation

APR = 0.36(SNGFR) + 3.9 ($r = 0.82$; $P < 0.01$) while the dashed line calculated for NSN values is given by the equation APR = 0.43(SNGFR) − 1.9 ($r = 0.82$, $P < 0.01$). The slope for the control data (0.36± 0.06) is not significantly different from that for the data of the NSN rats (0.43±0.02, $P > 0.2$). All values for NSN rats fall below the linear regression line for control animals while only two values from control rats fall below the NSN regression line.

In 6 control and 11 NSN rats both plasma and hilar lymph samples were obtained. The measured values of C and A/G ratios together with the calculated oncotic pressures of these samples are shown in Table IV. Although no significant alterations between groups were noted in systemic (C_A) or hilar lymph (C_L) protein concentartions, A/G ratios for both C_A and C_L were significantly reduced in NSN, relative to control values. These reductions in A/G ratios did not, however, significantly alter the calculated values of either π_A or π_L.

DISCUSSION

The method of induction of glomerulonephritis employed in the present study has previously been shown by us (15) to produce a remarkably uniform lesion which is confined solely to the glomerular capillary network. As evidenced by light, immunofluorescence, and electron microscopy, the lesion involved all glomeruli that were examined, and an autologous phase of immunological injury developed in each rat. Despite histologic evidence of extensive glomerular injury, the kidneys appeared normal at the time of micropuncture, and glomerular filtration rates (single nephron and whole kidney) were not significantly different from values in control rats. Although filtration rates were normal in NSN rats, SNFF and π_E were reduced significantly from values in control rats, despite an increase in $\overline{\Delta P}$. This was so because of a marked fall in the glomerular capillary K_f, on average to 0.026 nl/(s·mm Hg), or one-third that found for the normal rat (23).

TABLE III
Summary of the Measured Determinants of Proximal Tubule

					Control				
Animal no.	P_T	P_E	P_C	C_E	π_E	Q_E	SNGFR	$(TF/P)_{In}$	APR
		mm Hg		*g/100 ml*	*mm Hg*		*nl/min*		*nl/min*
1	10	12	8	7.6	29	35.1	20.6	2.22	11.3
2	10	16	8	8.5	35	79.6	41.2	1.98	20.0
3	11	16	8	8.0	32	62.6	41.7	1.56	14.8
4	12	18	12	7.9	31	48.7	31.4	2.02	17.0
5	12	16	10	7.5	28	81.2	36.0	1.58	13.1
6	11	12	6	8.1	32	52.1	30.6	2.00	15.3
7	10	15	7	8.2	33	83.0	38.6	2.17	20.9
8	10	15	7	9.1	39	37.2	29.2	2.58	17.0
9	13	13	7	7.9	31	44.8	21.1	2.42	11.8
10	10	11	6	7.6	29	65.2	22.9	1.82	10.1
11	11	12	6	8.1	32	52.1	30.6	2.00	15.3
12	14	12	10	7.5	28	91.2	37.2	1.83	17.1
13	9	13	8	9.2	40	33.3	24.2	2.49	14.4
14	11	13	8	8.5	35	38.8	20.9	1.95	10.1
15	10	13	7	9.0	38	20.3	18.0	1.95	9.2
16	9	15	8	8.1	32	36.5	31.0	2.12	16.4
17	10	11	9	8.2	33	40.2	30.3	1.95	13.3
18	9	14	9	8.2	33	36.3	17.9	2.44	10.2
Mean	10.7	13.8	8.0	8.2	32.8	52.1	29.1	2.06	14.3
	±0.3	±0.5	±0.4	±0.1	±0.8	±4.8	±1.8	±0.07	±0.8
	(18)	(18)	(18)	(18)	(18)	(18)	(18)	(18)	(18)
P value*									

Values are summarized as means±1 SE. The number of rats studied is given in parentheses.

The upper panels of Fig. 2 summarize the transcapillary driving forces for glomerular ultrafiltration in control and NSN rats. In control rats P_{UF_A} averaged approximately 17 mm Hg. By the efferent end of the capillary the transcapillary osmotic pressure difference ($\Delta\pi$) rose to a mean value which, on average, was identical to $\overline{\Delta P}$, denoting achievement of filtration pressure equi-
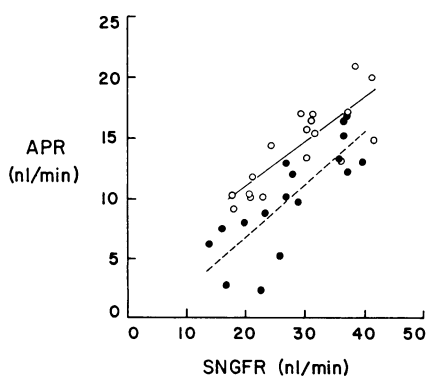

FIGURE 1 Comparison of mean values of APR plotted as a function of SNGFR in control (open circles) and NSN rats (closed circles). Regression lines are calculated by the method of least squares.

librium. The oncotic pressure profile in the upper left-hand panel of Fig. 2 was computed from the mean data for control animals (Table II), assuming a K_f value of 0.08 nl/(s·mm Hg), the value previously obtained in normal Wistar rats (23). This value of K_f yielded equilibrium near the efferent end of the capillary, indicating that K_f in the control rats of the present study was, on average, no less than that previously found for the normal Wistar rat. As seen in the upper right-hand panel of Fig. 2, in NSN rats P_{UF_A} was nearly twice that in controls, averaging 26 mm Hg. Because of the marked reduction in K_f, however, $\Delta\pi$ at the efferent end of the capillary failed to reach the value of $\overline{\Delta P}$, despite a greater initial driving force for ultrafiltration. $\overline{P}_{UF}$ (denoted by the shaded areas of the upper panels in Fig. 2) was nearly three times greater in NSN rats than in controls, averaging 17.8 mm Hg in the former compared with a maximum estimate of 6.2 mm Hg in the latter. These profiles of glomerular oncotic and hydraulic pressure differences are very similar to those reported by us previously for control and NSN rats (15).

In addition to the marked reduction in SNFF and π_E, Q_E and P_C were slightly but significantly increased in NSN rats, relative to values in control rats (Table III).

1320   *Maddox, Bennett, Deen, Glassock, Knutson, and Brenner*

Animal no.				Glomerulonephritis					
	P_T	P_E	P_C	C_E	π_E	Q_E	SNGFR	(TF/P)$_{In}$	APR
		mm Hg		*g/100 ml*	*mm Hg*	*nl/min*			*nl/min*
19	10	16	13	6.2	21	52.3	13.9	1.84	6.2
20	12	13	8	6.8	25	48.9	16.0	1.92	7.5
21	11	13	11	8.6	32	58.5	26.8	1.78	10.1
22	12	14	10	8.2	33	47.2	28.9	1.53	9.8
23	11	14	11	8.0	31	63.0	37.0	1.64	12.2
24	10	13	10	7.7	30	86.5	37.0	1.84	16.8
25	12	13	10	6.8	25	129.8	36.6	1.82	16.4
26	12	14	10	6.4	23	103.2	25.8	1.30	5.2
27	11	17	10	6.8	23	25.2	16.8	1.22	2.8
28	12	18	13	7.8	30	121.0	22.2	1.11	2.3
29	11	11	10	7.3	27	95.4	26.9	1.92	13.0
30	11	13	10	8.8	37	34.7	23.1	1.63	8.8
31	11	11	7	6.7	24	46.1	19.7	1.68	8.0
32	12	16	11	6.7	24	107.1	39.6	1.48	13.0
33	10	11	8	7.4	27	94.4	36.7	1.77	15.3
34	14	16	8	7.6	29	71.7	27.9	1.78	12.0
35	12	14	8	6.5	23	76.1	35.8	1.60	13.2
	11.4	13.9	9.9	7.3	27.3	74.2	27.7	1.64	10.2
	±0.2	±0.5	±0.4	±0.2	±1.1	±7.5	±2.0	±0.06	±1.1
	(17)	(17)	(17)	(17)	(17)	(17)	(17)	(17)	(17)
	>0.1	>0.5	<0.005	<0.001	<0.001	<0.025	>0.5	<0.001	<0.005

* As defined for Table I.

The lower panels of Fig. 2 summarize the transcapillary driving forces governing peritubular capillary uptake of proximal tubule reabsorbate in control and NSN rats. In control rats, after a large drop in hydraulic pressure along the efferent arteriole, the transcapillary oncotic pressure difference ($\pi_E - \pi_i$) at the beginning of the peritubular capillary network greatly exceeded the transcapillary hydraulic pressure difference ($P_C - P_i$). π_i was assumed to be equal to that calculated for hilar lymph (footnote 2 and Table IV), and P_i, the interstitial hydraulic pressure, was assumed to be approximately 0.[5] In NSN rats $\Delta\pi$ was considerably less than in controls due to the lower value of π_E in the former (lower right-hand panel, Fig. 2). ΔP was slightly greater in NSN than in controls because of the higher mean value of P_C, P_i assumed to be the same in NSN as in control rats. Thus the area between the $\Delta\pi$ and the ΔP profiles, denoting the mean net driving force for reabsorption, $\overline{P}_r$, was considerably less in NSN than in controls. In both groups, the imbalance between oncotic and hydraulic pressure differences continues to favor net fluid

[5] P_i in the rat has generally been found to be in the range of 0-4 mm Hg (27, 33).

reabsorption along the entire peritubular capillary network.

The quantitative effects of the observed changes in π_E, Q_E, and P_C on APR were examined by using a mathematical model of peritubular capillary uptake of reabsorbate (28). APR may be expressed as the product of the mean driving force for peritubular capillary fluid uptake ($\overline{P}_r$) and a reabsorption coefficient (K_r):

$$APR = K_r \cdot \overline{P}_r \qquad (13)$$

From the mean values of APR, Q_E, π_E, and P_C shown in Table III for control rats, assuming π_i to be approximately 4 mm Hg (footnote 2 and Table IV) and letting P_i be 0 (Footnote 5), we computed K_r to be approximately 0.016 nl/(s·mm Hg), in close agreement with that previously found in this laboratory for the normal Sprague-Dawley rat (28). Assuming that the values of K_r and $\pi_i - P_i$ did not change in NSN rats from control, a value of APR for NSN rats was calculated from the measured values of Q_E, π_E, and P_C shown in Table III. With this assumed value for $\pi_i - P_i$ of 4 mm Hg, APR was calculated to fall to 10.4 nl/min, in excellent agreement with the measured mean value of 10.2 nl/

TABLE IV

Summary of Measured Values of Plasma and Hilar Lymph Protein Concentrations and
A/G Ratios in Control and Experimental Animals

	Plasma			Hilar lymph		
	C_A	A/G	π_A	C_L	A/G	π_L*
	g/100 ml		mm Hg	g/100 ml		mm Hg
Control	4.9	1.02	15.2	1.4	2.72	3.9
	±0.1	±0.04	±0.4	±0.1	±0.25	±0.4
	(6)	(6)	(6)	(6)	(6)	(6)
Glomerulonephritis	5.1	0.74	16.3	1.4	1.35	3.4
	±0.1	±0.05	±0.6	±0.1	±0.12	±0.3
	(11)	(11)	(11)	(11)	(11)	(11)
P value‡	>0.2	<0.005	>0.2	>0.5	<0.001	>0.2

Values are expressed as means±1 SE. The number of rats studied is given in parentheses.
* π_L is assumed to equal π_I, the interstitial colloid osmotic pressure (see footnote 2).
‡ As defined for Table I.

min for NSN rats. To test the sensitivity of this calculation to the assumed value of $\pi_I - P_I$, APR was computed for NSN rats by using $\pi_I - P_I$ values ranging from 0 to 8 mm Hg, with the results given in Table V. For any given value of $\pi_I - P_I$, a value of K_r is determined which yields the measured value of APR in control rats, 14.3 nl/min. Thus, larger assumed values of

FIGURE 2 Comparison of ΔP and Δπ profiles along idealized glomerular and peritubular capillaries in control and NSN rats. See text for details.

$\pi_I - P_I$ (corresponding to smaller values of $\bar{P}_r$) require larger values of K_r, as shown in Table V. For each pair of $\pi_I - P_I$ and K_r values, the calculated value of APR for NSN rats was within ±1 SE of the observed APR for NSN animals (Table V), indicating that the close correspondence between calculated and observed values of APR for NSN rats was not critically dependent on the assumed values of $\pi_I - P_I$. These findings suggest that the observed changes in π_E and Pc were sufficient to offset the effect of the increase in Q_E and that the control of APR in NSN rats is mediated by the same peritubular factors that have been found to regulate APR under normal physiological conditions (5–14, 28).

The lesion produced in the present study was remarkably homogeneous from nephron to nephron in a given kidney, both morphologically and functionally. It is this functional homogeneity which allows us to characterize the behavior of a representative nephron from measurements made in a number of separate tu-
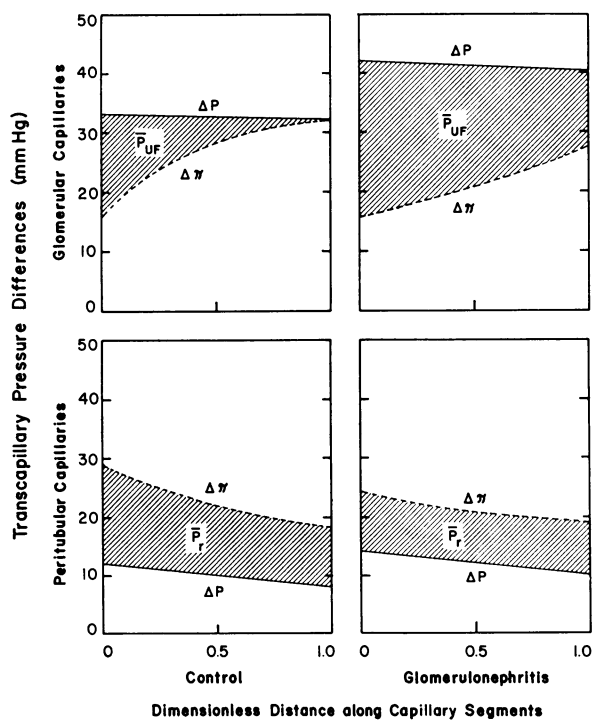
TABLE V

Calculated and observed Values of Absolute Proximal Reabsorption in NSN Rats at Different Assumed Values of $\pi_I - P_I$

$\pi_I - P_I$	K_r	Calculated APR
mm Hg	nl/(s·mm Hg)	nl/min
0	0.013	11.1
2	0.014	10.8
4	0.016	10.4
6	0.018	9.9
8	0.023	9.4
Observed APR (Table III)		10.2±1.1

bules and capillaries. A number of previous studies by others (1–4), utilizing a more severe model of glomerulonephritis in the rat, showed considerable diversity of nephron function and structure within each kidney. In each of these studies some degree of coupling between glomerulus and tubule function was found in that proximal fractional reabsorption (APR/SNGFR) was relatively constant from nephron to nephron in NSN rats, despite marked variations in SNGFR within each kidney. In accord with the present results, however, values reported for proximal fractional reabsorption in NSN rats (2–4) have generally been found to be lower than those seen in the normal rat.

In rats with relatively severe NSN and marked variations in SNGFR and APR among nephrons, the precise mechanism whereby APR changes with variations in SNGFR is not readily apparent from the available data. In the normal rat, there is a considerable body of evidence which indicates that the proximal tubule is endowed with little intrinsic capacity for regulation of sodium and water reabsorption (34–43) and that the control of APR is governed primarily by alterations in the peritubular transcapillary Starling forces (5–14, 28). The data obtained in the present study indicate that APR in rats with a moderate degree of NSN is likewise governed largely by the peritubular environment, and in particular, by the extent to which π_E is reduced. Unfortunately, a rigorous analysis of the role of the peritubular transcapillary Starling forces in governing APR in the more advanced stages of NSN studied by others (1–4) cannot be performed since few, if any, of the determinants of peritubular transcapillary fluid exchange were measured. It is worthy of note that in two studies (2, 3), however, estimates of an average value of π_E can be made since whole kidney filtration fraction (FF) and systemic protein concentration (C_A) were measured. In accord with the results of the present study, FF was lower, on average, in NSN rats than in normal rats. Since values for C_A were reported to be less than or equal to those in the normal rat, this reduction in FF indicates that π_E, on average, likewise must have been reduced. In the study of Allison, Wilson, and Gottschalk (2), $\overline{\Delta P}$ and Q_A, estimated from indirect measurements, were noted to vary markedly from nephron to nephron in a given animal. Since SNFF is determined, in part, by these quantities (32, 44), it is unlikely that SNFF was uniform from nephron to nephron. Hence it is probable that substantial variations in π_E and Q_E occurred among nephrons in their study, thereby making it extremely difficult to assess the extent to which variations in the local peritubular environment might have been responsible for their observed variations in APR among nephrons.

In the more advanced states of NSN, since C_A is likely to be normal or reduced, variations in SNGFR among nephrons must result from nonuniform reductions in Q_A, K_f, $\overline{\Delta P}$, or a combination of these factors (32, 44). These changes would tend to reduce π_E and/or Q_E. In either case the peritubular transcapillary forces governing APR would be altered so as to reduce APR; and, in general, the greater the fall in SNGFR, the more marked the reduction in APR. Future studies should therefore rely on direct measurements of SNGFR, APR, Q_E, π_E, and P_C within a given nephron unit when heterogeneity of function exists in order to determine the extent to which the control of APR is mediated by the peritubular transcapillary driving forces in chronic stages of glomerulonephritis.

In the present study fractional urinary sodium excretion in NSN rats was found not to differ, on average, from values in control rats. If we assume the behavior of the surface nephrons that were studied to be representative of that for nephrons throughout the kidney, the finding that SNGFR was also the same in NSN as in controls but that proximal fractional sodium reabsorption was significantly depressed in NSN indicates that sodium reabsorption in segments distal to proximal tubule puncture sites must have been increased in NSN. Whether the abnormally high fractional sodium reabsorption seen in patients with acute glomerulonephritis is similarly due to enhanced reabsorption at sites distal to the proximal tubule remains to be determined.

ACKNOWLEDGMENTS

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