Pathogenesis of Glomerular Injury in the Fawn-Hooded Rat: Effect of Unilateral Nephrectomy$^{1,2}$

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ABSTRACT

Fawn-hooded (FH) rats with congenital proteinuria and systemic and glomerular hypertension are very susceptible to renal damage at a young age. In this study, the effects of unilateral nephrectomy (UNX) on the function and structure of the remaining kidney in the FH substrain were assessed. A long-term study was performed to determine the changes in systemic blood pressure, renal function, and proteinuria during the development of chronic renal failure in UNX-FHH and two-kidney (2K) FHH rats. Renal micropuncture and morphologic studies were performed at 4 wk after surgery. The long-term study showed that, after UNX, systolic blood pressure did not differ significantly from that of 2K-FHH rats. After UNX, there was compensatory hyperfiltration, at about 70% of the 2K level, that could be maintained for 12 wk only. The subsequent fall in GFR was preceded by severe proteinuria. The mean survival time of UNX-FHH rats was only 35 wk. Micropuncture studies showed that the high mean glomerular capillary pressure of 2K-FHH rats was further elevated after UNX. The glomerular capillary ultrafiltration coefficient did not differ significantly between UNX-FHH and 2K-FHH rats. The weight of the remaining kidney and the mean glomerular tuft volume in UNX-FHH were, on average, 36 and 31% greater than in 2K rats. The results indicate that the FHH rat is extremely vulnerable to the adverse renal effects of UNX. A comparison of the hemodynamic and structural data of this study with those reported for other rat strains indicated that the severe glomerular hypertension, but not the degree of glomerular hyperfiltration, underlies the high susceptibility to renal damage in UNX-FHH rats.

Key Words: Glomerular capillary hydraulic pressure, GFR, proteinuria, focal and segmental glomerular sclerosis, chronic renal failure

The rate of development of chronic renal failure (CRF) in renal ablation models varies directly with the amount of excised and/or infarcted kidney tissue (1,2) and with the corresponding maladaptive increase in mean glomerular capillary hydraulic pressure ($P_{oc}$) (3-7). In general, after a variable period of compensatory glomerular hyperfiltration, nephron loss results in progressive focal and segmental glomerular sclerosis (FGS) and CRF. However, marked differences have been described in the susceptibility of different rat strains to the development of long-term sequelae after ablation (8-11), suggesting that genetic factors also influence the rate of progression of CRF in such models.

The fawn-hooded (FH) rat exhibits a remarkable susceptibility to develop FGS spontaneously at a young age (12,13). This is associated with moderate systemic hypertension (13,14), increased urinary protein excretion ($U_{p}V$) (12-16), glomerular hypertension (17), and glomerular hyperfiltration (15,16). FGS and proteinuria progress, and eventually, animals die as a result of ESRD (13,16). We recently detected the spontaneous occurrence of glomerular capillary hypertension and hyperfiltration in two inbred sub-strains of FH rats and were able to predict the development of FGS according to the level of $P_{oc}$ (17). Excessive efferent arteriolar resistance in associa-
tion with elevated systemic blood pressure proved to be responsible for the observed glomerular capillary hypertension. For inbreeding, FH rats were selected on the basis of the differences in values for awake systolic blood pressure (SBP) (18). Rats with the highest values for SBP were designated FHH, and those with lowest were designated FHL. FHH rats were shown to have higher values for \( U_2V \), \( P_{OC} \), and single-nephron (SN) and whole-kidney GFR and more rapid development of FGS and CRF than FHL animals (16–18).

The purpose of this study was to assess the effects of unilateral nephrectomy (UNX) on the structure and function of the remaining kidney of the FHH sub-strain. A long-term study was done to determine the changes in renal function, proteinuria, and systemic blood pressure during the development of CRF in both UNX- and two-kidney (2K)-FHH rats. At 4 wk after surgery, renal micropuncture studies were also performed to ascertain the magnitude of changes in glomerular hemodynamics induced by the UNX state. Morphologic studies were done in kidney tissue from rats used for these microcirculatory studies.

**MATERIALS AND METHODS**

**Animals**

FHH rats were bred at the animal facilities of Erasmus University, Rotterdam, the Netherlands. Inbreeding procedures have been described in detail previously (18). All rats received standard rat chow (26% protein) and tap water ad libitum.

**Surgery**

Rats were anesthetized with ethyl ether, and the right kidney was removed after exposure by a midline incision of the abdominal wall and careful separation from the adrenal gland and associated connective tissue (UNX). A sham operation was performed in which the right kidney was gently manipulated but otherwise left intact (2K).

**Long-Term Study**

Long-term studies were performed at the Laboratory for Surgery, Rotterdam. Twenty-eight weight-matched male FHH rats were operated on at the age of 4 to 5 wk (2K, \( N = 14 \); UNX, \( N = 14 \)). After surgery, body weight and awake SBP were monitored every 2 wk. GFR and effective RPF (ERPF) were determined as the plasma clearance of \(^{51} \text{Cr} \)-EDTA and \(^{125} \text{I} \)-iodohippurate, respectively, and were determined every 6 wk. The method has been described in detail elsewhere (19). Briefly, from pentobarbital-anesthetized rats (60 mg/kg, ip), a single, timed blood sample was obtained 60 min after the iv injection of pre-counted amounts of the radioactive markers. The method allows for repeated measurements within the same animal. In plasma samples obtained during GFR measurement, the creatinine (\( P_Cr \)) and urea (\( P_U \)) levels were assessed by standard clinical chemical techniques. Urine was collected from individual rats during two successive 24-h periods for the determination of \( U_2V \). Total urinary protein concentration was measured colorimetrically (20). The SBP was measured by indirect tail-cuff plethysmography in awake, restrained animals.

**Micropuncture Study**

Micropuncture study was performed in the Renal Division at the Brigham and Women's Hospital, Boston, MA. Animals were shipped from Rotterdam to Boston at the age of 4 to 5 wk and underwent operations at the age of 8 wk (2K, \( N = 8 \); UNX, \( N = 7 \)). The composition of the rat diets in Rotterdam and Boston were comparable. Micropuncture experiments were performed when the rats were 12 wk old. One week before experimentation, total \( U_2V \) over a 24-h period was determined. Immediately after the completion of the micropuncture experiment, kidney(s) were perfusion fixed for morphologic studies.

After the induction of anesthesia with ethyl ether, rats were positioned on a temperature-regulated micropuncture table and were subsequently given Inactin (BYK Gulden, Konstanz, Germany) (100 mg/kg body wt, ip). A rectal probe was inserted to monitor temperature, which was maintained at 37.0 ± 0.5°C. Tracheostomy was performed, and a left femoral artery catheter was inserted to monitor arterial blood pressure and to obtain arterial blood samples. After the collection of a baseline blood sample, the right jugular vein was cannulated for the infusion of plasma and insulin. The plasma volume of rats prepared for micropuncture is reduced by about 20% (21). In order to study the rats in an euvoletic state, isoncotic plasma obtained from normal adult Sprague-Dawley rats was infused iv at a rate of 0.1 mL/min to a total amount equal to 1% of the body weight. Thereafter, plasma infusion was continued at a rate of 0.58 mL/h to maintain a near-constant hemato-crit. Insulin (10 g/dL for 2 K rats and 5 g/dL for UNX rats) in 0.9% NaCl was infused iv at a rate of 1.2 mL/h. The bladder was drained in 2K rats. The left kidney was exposed and suspended on a lucite holder, with its surface illuminated and bathed with isotonic saline. The left ureter was cannulated. A 60-min equilibration period was allowed after completion of the fast plasma infusion.

For the calculation of single-nephron GFR (SNGFR), three to six exactly timed samples of fluid were collected from superficial proximal tubules for the determination of flow rate and insulin concentration. Three to six effenter arteriolar blood samples were obtained from superficial star vessels for the determination of effenter arteriolar protein concen-
tration. Coincident with these collections and the hydraulic pressure measurements, arterial blood samples were obtained for the determination of hematocrit and plasma concentrations of insulin and protein, and 10- to 20-min urine collections from the left kidney were obtained for the determination of flow rate and inulin concentration. These measurements permitted the calculation of the GFR by standard formula.

Time-averaged hydraulic pressures were measured directly in efferent arterioles \( (P_e) \) and in superficial proximal tubules under free-flow \( (P_f) \) and stop-flow \( (P_{SF}) \) conditions with a servo-null micropipette transducer system (Model 5A; Instrumentation for Physiology and Medicine, San Diego, CA). Stop-flow conditions were obtained by the injection of bone wax (Ethicon W-31G, Brigham and Women’s Hospital, Boston, MA) into proximal tubules with a wax-blocking device (Research Instruments & Mfg, Corvallis, OR). At least three to four \( P_{SF} \) recordings in different nephrons, with a minimum duration of 2 to 4 min each, were obtained during each experiment. The mean \( P_{OC} \) was calculated as follows (22).

\[
P_{OC} = P_{SF} + P_{SF}
\]

The colloid osmotic pressure of plasma entering and leaving the glomerular capillaries was estimated from values for protein concentration in femoral arterial (representing afferent arteriolar) and star vessel (representing efferent arteriolar) plasma (23). The estimates of pre-\( (C_a) \) and post-\( (C_s) \) glomerular protein concentration permit the calculation of single nephron filtration fraction (SNFF). Femoral arterial plasma protein concentrations were measured separately during the microsampling period \( (C_a) \) and during micropressure measurements \( (C_{SF}) \). Glomerular capillary ultrafiltration coefficient \( (K_f) \), afferent and efferent arteriolar resistances \( (R_a \text{ and } R_e) \), and initial glomerular capillary plasma flow rate \( (Q_0) \) were calculated (23). The mean transcapillary hydraulic pressure difference \( (\Delta P) \) was calculated as:

\[
\Delta P = P_{OC} - P_f
\]

The volume of 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 tubule fluid insulin concentration was measured by a microfluorescence method (24). Insulin concentrations in plasma and urine were measured by a macroantherne method (25). Protein concentrations in efferent arteriolar blood samples were determined by a fluorometric method (26).

Renal Morphology

After the completion of the micropuncture experiment, the kidneys were perfusion fixed at the measured SBP for 2 to 3 minutes with 1.25% glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.4). Kidney weight was noted. Two midcoronal slices, one of each kidney, of 2- to 3-mm thickness, were processed for light microscopic examination. Paraffin sections (3-μm thick) were stained with hematoxylin and eosin and with periodic acid–Schiff reagent.

The extent of glomerular damage was determined on periodic acid-Schiff-stained slides by counting on two coronal sections all glomerular profiles with segmental or global collapse of capillaries, with or without associated hyalin deposition and adhesion of the tuft to Bowman’s capsule. The extent of FGS was expressed as the percentage of glomeruli with sclerotic lesions.

The average glomerular tuft volume \( (V_o) \) for each animal was determined by the procedure described by Weibel (27). For this purpose, the mean glomerular random cross-sectional area \( (\bar{A}_o) \) was determined on 50 systematically sampled glomerular tuft profiles by point counting at a final magnification of ×200 with a 361-point ocular grid covering a 369,664-μm² microscopic field. \( V_o \) was then calculated as \( V_o = (\beta/k)(\bar{A}_o)^{5/2} \), where \( \beta = 1.38 \) is the shape coefficient for spheres (the idealized shape of glomeruli) and \( k = 1.1 \) is a size distribution coefficient (27).

Statistics

All data are given as mean ± SE. A t test was applied to detect differences between the mean values of 2K and UNX rats in the long-term, the microcirculatory, and the morphologic studies. Statistical significance was defined as \( P < 0.05 \).

RESULTS

Long-Term Studies

SBP increased in both 2K and UNX rats, but no significant differences were found between groups at any time (Figure 1). Initially, values for GFR and ERPF in UNX animals showed a compensatory rise of 40 and 60%, respectively, as compared with single-kidney values in 2K rats (Figure 2). However, from week 12 onwards, GFR and ERPF showed a rapid decline, and eventually all UNX animals died as the result of end-stage renal failure. Mean survival time was 35 ± 7 wk (median, 34 wk) post-UNX.

UNX initially resulted in slightly higher values for \( P_e \) and \( P_{ar} \) compared with those found in 2K rats (Table 1). Values for \( P_e \) and \( P_{ar} \) increased steadily from week 12 onwards in the UNX animals, whereas values for these parameters remained unaltered in 2K rats during the complete follow-up period.

In UNX rats, the declines in GFR and ERPF were
Renal Morphology

Results are summarized in Table 3. Left kidney weight and mean glomerular tuft volume in UNX rats were, on average, 36 and 31% greater, respectively, than in 2K rats ($P < 0.05$). Values for FGS were only numerically higher in UNX rats at the age of 12 wk.

DISCUSSION

This study demonstrates the remarkable susceptibility of the remaining kidney in UNX-FHH rats to progress rapidly to end-stage renal failure. The mean survival time post-UNX of 35 wk in these animals is approximately one third of that observed in a non-motensive strain (WAG) submitted to UNX (28). A stable GFR post-UNX in WAG rats is present for 48 wk, but this period of stability is reduced to only 12 wk in FHH rats. A rate of decline in GFR could not be estimated for individual rats in this study, because more frequent measurements are required for such calculations. However, the changes in the mean GFR accompanied by a marked increase in $U_pV$ (Figure 3). Proteinuria was also present in 2K rats, but to a much lower degree. Because of the marked reduction in the GFR of UNX rats after week 24, there was a slight decrease in the level of proteinuria.

Micropuncture Studies

Results are summarized in Table 2. One week before the acute micropuncture study, $U_pV$ was elevated in UNX as compared with 2K animals, averaging 65 ± 13 and 26 ± 3 mg/24 h, respectively ($P < 0.05$). Values for SBP and mean arterial pressure were not statistically different, and SBP values for both groups were comparable to values found in the long-term study. SNGRF increased approximately 47% and FF tended to decrease, as a consequence of UNX. No significant differences were found for $C_a$, $C_R$, and $C_{SP}$ among groups. Mean $P_{SP}$, mean $P_{OC}$, and mean $\Delta P$ were high in 2K rats, averaging 45 ± 0.8, 62 ± 1.0, and 49 ± 1.2 mm Hg, respectively. UNX caused a significant further increase in these parameters, averaging 51 ± 1.3, 67 ± 1.4, and 56 ± 1.5 mm Hg, respectively ($P < 0.05$). Filtration pressure disequilibrium (where $P_2 < \Delta P$) was present in all rats studied, and unique values for the glomerular capillary $K_f$ were calculated. $K_f$ averaged 0.041 ± 0.002 and 0.045 ± 0.003 mL/s-mm Hg for the 2K and UNX groups, respectively, and were not statistically different. Values for initial $Q_a$ in UNX rats increased by approximately 65% compared with that in 2K rats. Despite a significant decrease in values for $R_a$ and $R_e$ (36 to 37%), the abnormal balance between afferent and efferent arteriolar resistances, already present in 2K-FHH rats (17), was not altered as a consequence of UNX.
TABLE 1. Body weight, $P_c$, and $P_u$ in the long-term study

<table>
<thead>
<tr>
<th>Week</th>
<th>Body Wt (g)</th>
<th>$P_u$ (mmol/L)</th>
<th>$P_c$ (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2K</td>
<td>UNX</td>
<td>2K</td>
<td>UNX</td>
</tr>
<tr>
<td>6</td>
<td>252 ± 4 (14)</td>
<td>237 ± 5 (14)</td>
<td>4.9 ± 0.1</td>
</tr>
<tr>
<td>12</td>
<td>297 ± 4 (14)</td>
<td>280 ± 4 (14)</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>24</td>
<td>348 ± 4 (14)</td>
<td>319 ± 5 (1/13)</td>
<td>5.0 ± 0.2</td>
</tr>
<tr>
<td>36</td>
<td>373 ± 5 (14)</td>
<td>322 ± 6 (7/7)</td>
<td>5.5 ± 0.2</td>
</tr>
</tbody>
</table>

$^a$ Values are mean ± SE. Values in parentheses, number of rats; values in parentheses with shilling construction, number of rats dead due to CRF/number of rats measured. Throughout the study, the data for body weight, $P_u$, and $P_c$ of UNX rats were significantly different from those of 2K rats.

In UNX-FHH rats indicate a rate of decline of approximately 0.7 mL/min per 12-wk period, about three times faster than reported by us in UNX-WAG (28). The amount of proteinuria post-UNX was also much higher in FHH than in WAG animals. In UNX-FHH, the highest value for $U_p$, more than 400 mg/day, was achieved at 24 wk post-UNX, whereas the maximum value for $U_p$ in UNX-WAG was 250 mg/day at 72 wk post-UNX (28). In accord with previous studies, UNX did not increase blood pressure. However, at 4 wk post-UNX, the glomerular hemodynamics, already altered in 2K-FHH rats with a normal number of nephrons (17), became further abnormal. The average increase in SNGFR in UNX-FHH animals of 47% was comparable to the increase in total GFR found in the long-term study group. The $\Delta P$ was increased on average by 7 mm Hg, to 56 ± 1.5 mm Hg. Values found for $K_f$ were similar in both 2K and UNX groups. The $V_0$ can be used as a rough indicator of glomerular tuft area available for filtration. Because $V_0$ increased and $K_f$ remained the same after UNX, pore parameters defining molecular membrane conductivity must have been altered. A decrease in pore density and/or an increase in pore length could explain the unaltered $K_f$. Values for $R_A$ and $R_e$ decreased proportionally as a consequence of UNX. Therefore, the anomalous balance between preglomerular and postglomerular resistance, present in 2K-FHH animals, remained unmodified.

Various mechanisms of glomerular adaptation to initial injury have been proposed as important in the cause and/or mediation of progressive CRF. Brenner and coworkers have postulated that intraglomerular circulatory adaptation to nephron loss and/or injury, notably an increase in $P_{GC}$, is the main driving force for continuous glomerular damage (4). This hypothesis has been confirmed in numerous experimental studies of renal ablation (3,4,7) as well as in other experimental models. In these models, $P_{GC}$ is increased from the onset of the disease, and maneuvers that lower $P_{GC}$ protect the kidney from FGS. Recently, the congenital occurrence of glomerular capillary hypertension in FH rats was found to predict the subsequent development of increased $U_p$, FGS, and CRF. Therefore, even if an animal has a normal number of nephrons, glomerular capillary hypertension can be present and this inborn glomerular hypertensive state can lead to progressive CRF (17). In recent years, others have surmised that growth promoters cause glomerular hypertrophy and mesangial matrix accumulation (29,30) and may play a role in the progressive destruction of glomerular ultrastructure and function. Finally, an altered permeability of the glomerular capillary membrane to macromolecules has been postulated to contribute to glomerulosclerosis (31).

In this study, we did not compare FHH animals with a strain that is less susceptible to develop FGS and CRF. Previous studies have established variability among rat strains in susceptibility to develop FGS (6,10,11). However, none of these studies assessed both glomerular hemodynamics and morphologic parameters. We are aware that comparison with data...
reported from other laboratories might be speculative. Nevertheless, we will do so in order to reveal potential differences in the responses of FHH and other less-susceptible rat strains to UNX.

At 4 wk post-UNX, FHH rats developed a marked degree of glomerular capillary hypertension. The average $P_{OC}$ value of 67 mm Hg in these animals is much higher than those reported for uninephrectomized Munich Wistar (MW) (3,32) or Wistar Kyoto (WKY) rats (6), which range from 50 to 55 mm Hg. Both strains are not very susceptible to the development of renal damage in the remaining kidney post-UNX (6,11,33,34). The level of glomerular hypertension in UNX-FHH, however, is comparable to that reported for MW rats with remnant kidneys (3,34), in which renal damage typically progresses rapidly.

At 4 wk post-UNX, the degree of hyperfiltration at the whole-kidney level in UNX-FHH amounted to about 140% of the single-kidney value in 2K rats. The magnitude of the compensatory increase in FHH rats is therefore not substantially different from the increase reported for many other rat strains (6,10,11,32) that are less susceptible to FGS and CRF post-UNX than are FHH rats. Consequently, the magnitude of the relative increase in GFR post-UNX cannot explain the differences in susceptibility to renal damage. However, the absolute level of glomerular hyperfiltration post-UNX may be higher in FHH than in other strains. The value found in this study, 92 ± 6 nL/min (Table 3), is indeed much higher than that usually reported for UNX rats of other strains (5,6,32). Similarly, a $Q_a$ value of 300 ± 19 nL/min for UNX-FHH (Table 3) is higher than that reported for other strains. Like the values for $P_{OC}$, those for $Q_a$ determined in UNX-FHH are closer to those reported for glomeruli remaining after three-fourths or five-sixths nephrectomy in MW rats (7,34) than to those of UNX-MW rats (5,32).

The magnitude of weight change of the remaining kidney at 4 wk post-UNX in FHH is comparable with values previously reported for WAG rats (35). The 40% average increase in kidney weight is similar to the values reported in other strains (10,11,32). Therefore, whole-kidney hypertrophy does not explain the increased susceptibility of the FHH strain to develop renal damage post-UNX. On the glomerular level, increases in both $V_0$ and absolute values for $V_0$ post-UNX in FHH were similar to those reported in other strains post-UNX (10,11). Thus, glomerular hypertrophy appears to be unimportant when accounting for differences in susceptibility between strains.

The question still remains unsolved whether compensatory glomerular growth promoters or hemodynamic alterations cause glomerular volume to increase post-UNX. Hemodynamic adaptation occurs immediately post-UNX, as demonstrated by the increase in both whole-kidney (35,36) and SNGFR, (36)

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**TABLE 2. Summary data of micro puncture study**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>12P</th>
<th>MAP</th>
<th>Hct</th>
<th>SNGFR</th>
<th>SNFF</th>
<th>Ccr</th>
<th>Cmax</th>
<th>α</th>
<th>Cr</th>
<th>$P_{OC}$</th>
<th>$\Delta P$</th>
<th>$P_{OC}$</th>
<th>$\Delta P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2K</td>
<td>6</td>
<td>25</td>
<td>122</td>
<td>44</td>
<td>62.6</td>
<td>0.34</td>
<td>10.2</td>
<td>0.2</td>
<td>31</td>
<td>16</td>
<td>51.4</td>
<td>7.5</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>UNX</td>
<td>7</td>
<td>16</td>
<td>45</td>
<td>92.1</td>
<td>0.34</td>
<td>10.1</td>
<td>0.1</td>
<td>31</td>
<td>16</td>
<td>51.4</td>
<td>7.5</td>
<td>1</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

* Values are means ± SE. *P = 0.05 versus 2K rats. 

$P_{OC}$, mean effective arterial pressure; $\Delta P$, mean effective arteriolar pressure; $\alpha$, sum of $R_2$ and $R_3$. See text for definitions of other abbreviations.
even before the increase in kidney weight is apparent. Furthermore, an early specific growth response of glomeruli is doubtful because the gene expression of growth-related proteins and extracellular matrix constituents was unaltered in isolated glomeruli during the first week post-UNX (37). However, because gene expression in total renal cortex was increased in a specific time-related fashion, this study confirmed earlier findings that renal growth post-UNX consists predominantly of hypertrophy of renal tubules, rather than of glomeruli (38). Finally, a morphologic study indicated that the glomerular lesions induced by UNX, i.e., the formation of irregular and giant capillary loops, were not the result of normal or compensatory growth but were secondary to failure of the mesangium (39). An increased wall tension, caused by hemodynamic changes, may initiate and maintain this capillary expansion. It may be of note that a 31\% increase in V\textsubscript{p}, as induced by UNX in this study, can be explained by just a 10\% increase in capillary diameter.

A comparison of the hemodynamic and structural changes of various rat strains after UNX strongly suggests the conclusion that the high susceptibility to develop renal damage in the UNX-FHH rat compared with other strains is defined by the levels of glomerular hypertension, hyperfiltration, and hyperperfusion, but not the degree of increase in glomerular size. The question remains whether these persistent adaptive hemodynamic changes in UNX-FHH account solely for the high susceptibility, or whether there is an additional role for altered permeability to macromolecules in the progressive renal damage? An increased permeability due to changes in size- and charge-selective properties of the glomerular capillary wall has been reported after UNX (40) and extreme ablation of renal mass (41). Proteinuria is a prominent feature in FHH rats. It is unclear whether this is solely the result of the elevated glomerular filtration pressure, flow, and filtration present in these animals, or whether alterations in size- and/or charge-selective properties of the glomerular wall and/or altered tubular handling of proteins are contributory. Substrains of FH rats with differences in U\textsubscript{p}V also differ in the rate of renal deterioration (16). The highest values for U\textsubscript{p}V and P\textsubscript{oc} were coincident in FHH animals, whereas in FHL rats, the lowest values for these parameters were linked (17). In FHH animals, the increased proteinuria is almost exclusively due to increased urinary albumin excretion (A.P. Provoost, unpublished observation). This excludes a prominent role for an impaired tubular handling of filtered proteins and might indicate a specific alteration in charge-selective properties of the filtration barrier. Studies of the permeability of the capillary wall of FHH rats to macromolecules are needed to determine a role for size- and/or charge-selectivity defects in the glomeruli of FHH rats. Preliminary data from such a study indicate that 2K-FHH rats have higher fractional clearances of polydisperse Ficoll, with a Stokes radius less than 50 Å, than those reported for MW rats (42,43). In UNX-FHH, there was no further change in size selectivity in the 20 to 40 Å range, suggesting that the more pronounced albuminuria post-UNX results from additional defects in charge selectivity (43).

Systemic hypertension in spontaneously hypertensive rats (SHR) is much higher than in FHH animals at a similar age. The hypertension in SHR is not transmitted in the glomerular capillary network, and FGS and renal failure are not early findings in this rat strain. However, when renal mass is reduced, the Rx decreases in SHR and allows the transmission of systemic hypertension into the glomerular capillary network (6). In UNX-FHH, there was no further change in size selectivity (6). In the study presented here, we found that intact FHH rats with relatively mild systemic hypertension have elevated values for P\textsubscript{oc}, and UNX causes a further increase in this parameter. An abnormal balance in Rx and Rx is present in intact FHH rats and is not altered by UNX. Renal vascular regulation of glomerular filtration might be genetically determined and thereby predispose to renal failure if P\textsubscript{oc} or ΔP is excessive. Recent studies in humans have identified

**TABLE 3. Summary of morphologic parameters**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Body Wt (g)</th>
<th>LKW (g)</th>
<th>TKW (g)</th>
<th>V\textsubscript{p} (10\textsuperscript{6} μm\textsuperscript{2})</th>
<th>FGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2K</td>
<td>8</td>
<td>278 ± 8</td>
<td>1.73 ± 0.10</td>
<td>3.43 ± 0.20</td>
<td>1.64 ± 0.04</td>
<td>3.8 ± 0.7</td>
</tr>
<tr>
<td>UNX</td>
<td>7</td>
<td>262 ± 8</td>
<td>2.35 ± 0.07\textsuperscript{b}</td>
<td>2.35 ± 0.07\textsuperscript{b}</td>
<td>2.15 ± 0.14\textsuperscript{b}</td>
<td>10.1 ± 2.9</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Values are means ± SE. N, number of rats; LKW, left kidney weight; TKW, total kidney weight.

\textsuperscript{b}P < 0.05 versus 2K rats.
genetic factors as an important independent risk factor for the development of ESRD, secondary to hypertension and diabetes (44,45). The different animal strains available for renal pathophysiologic studies in reference to FGS and CRF may allow us to identify such genetic determinants, as has been the case in rats with congenital hypertension (46).

In conclusion, after UNX, the FHH rat rapidly develops renal damage and this damage correlates with adaptive increases in glomerular pressure, plasma flow, and filtration rate, as well as in the size of the glomerulus. In our view, the hemodynamic changes, rather than the structural adaptation of the glomeruli, appear to underlie the high susceptibility to develop renal damage after UNX in FHH rats compared as with other rat strains.

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REFERENCES


27. Weibel ER: Stereological Methods: Practical Methods for Biological Morphometry. Vol 1. Lon-


