Altered renal hemodynamics and impaired myogenic responses in the fawn-hooded rat

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Van Dokkum, Richard P. E., Cheng-Wen Sun, Abraham P. Provoost, Howard J. Jacob, and Richard J. Roman. Altered renal hemodynamics and impaired myogenic responses in the fawn-hooded rat. *Am. J. Physiol.* 276 (*Regulatory Integrative Comp. Physiol.* 45): R855–R863, 1999.—The present study examined whether an abnormality in the myogenic response of renal arterioles that impairs autoregulation of renal blood flow (RBF) and glomerular capillary pressure (P_{GC}) contributes to the development of renal damage in fawn-hooded hypertensive (FHH) rats. Autoregulation of whole kidney, cortical, and medullary blood flow and P_{GC} were compared in young (12 wk old) FHH and fawn-hooded low blood pressure (FHL) rats in volume-replete and volume-expanded conditions. Baseline RBF, cortical and medullary blood flow, and P_{GC} were significantly greater in FHH than in FHL rats. Autoregulation of renal and cortical blood flow was significantly impaired in FHH rats compared with results obtained in FHL rats. Myogenically mediated autoregulation of P_{GC} was significantly greater in FHL than in FHH rats. P_{GC} rose from 46 ± 1 to 71 ± 2 mmHg in response to an increase in renal perfusion pressure from 100 to 150 mmHg in FHH rats, whereas it only increased from 39 ± 2 to 53 ± 1 mmHg in FHL rats. Isolated perfused renal interlobular arteries from FHL rats constricted by 10% in response to elevations in transmural pressure from 70 to 120 mmHg. In contrast, the diameter of vessels from FHH rats increased by 15%. These results indicate that the myogenic response of small renal arteries is altered in FHH rats, and this contributes to an impaired autoregulation of renal blood flow and elevations in P_{GC} in this strain.

autoregulation; renal blood flow; glomerular capillary pressure

THE FAWN-HOODED HYPERTENSIVE (FHH) rat is a genetic model of hypertension-associated renal disease that develops systolic hypertension, severe albuminuria, and focal glomerulosclerosis (FGS) (23). A closely related control strain of fawn-hooded low blood pressure (FHL) rats does not develop hypertension or renal disease. Previous studies have indicated that elevations in renal blood flow (RBF), glomerular filtration rate (GFR), and glomerular capillary pressure (P_{GC}) precede the development of glomerular disease in FHH rats (10, 25, 26). Recently, we reported that autoregulation of RBF and GFR is impaired in FHH rats (11). Previous studies by Simons et al. (25) indicating that

P_{GC} is related to the level of arterial pressure in FHH rats treated with various antihypertensive agents suggest that these animals fail to regulate afferent arteriolar resistance appropriately in response to changes in arterial pressure. Potentially, this could be due to an abnormality in tubuloglomerular feedback (TGF) and/or the myogenic mechanisms that regulate renal vascular tone in the preglomerular vasculature of the kidney.

In this regard, Verseput et al. (28) have recently reported that TGF responses are intact in FHH rats. Therefore, in the present study, we examined whether the myogenic response of the renal vasculature is altered before the development of glomerulosclerosis in young (12 wk old) FHH rats and whether this abnormality might contribute to an impairment in autoregulation of RBF and elevations in P_{GC} in these animals. Such a defect should be especially evident after acute volume expansion or in rats fed a high-salt diet, both of which diminish the contribution of TGF to autoregulation of RBF and GFR. Thus changes in RBF, cortical and medullary blood flow, and P_{GC} in response to elevations in renal perfusion pressure (RPP) were compared in volume-expanded and volume-replete 12-wk-old male FHH and FHL rats. In addition, the myogenic response of renal interlobular arteries microdissected from the kidneys of these animals was directly studied in vitro.

METHODS

General methods. Experiments were performed in male FHH and FHL rats matched for age and body weight. They were all 12 wk old and weighed ~300 g at the time of the acute experiments. FHH rats at this age do not yet exhibit significant FGS. The rats were obtained from colonies maintained at the Medical College of Wisconsin, which were derived from the original colony at the Erasmus University Rotterdam (FHH/EUR and FHL/EUR) maintained by Dr. Provoost. The rats were housed in an American Association for the Accreditation of Laboratory Animal Care approved animal care facility at the Medical College of Wisconsin and had free access to food and water throughout the study. On the night before the acute experiments, food intake was restricted to facilitate surgical procedures.

General surgical procedures. Rats were anesthetized with an intramuscular injection of ketamine (Ketaset; Fort Dodge Laboratories, Fort Dodge, IA) in a dose of 10 mg/kg, followed by a 30-mg/kg intraperitoneal injection of 5-*sec*-butyl-5-ethyl-2-thiobarbituric acid (Inactin; Byk-Gulden, Konstanz, Germany). The animals were placed on a servocontrolled heated surgical table to maintain body temperature at 37°C. The trachea was cannulated using PE-240 tubing to facilitate breathing, and cannulas were placed in the carotid and femoral arteries for measurement of arterial pressure above

and below the left renal artery using a model P23 Gould Statham pressure transducer (Recording System Division; Gould, Cleveland, OH) connected to a model RPS 7C8A Grass amplifier (Grass Instruments, Quincy, MA). Another catheter was placed in the left external jugular vein for constant intravenous infusion, and 1% BSA in 0.9% NaCl was infused at a rate of 100 μl/min throughout the experiment. Because the FHH and FHL rat strains have a bleeding disorder, we had to use a higher rate of infusion to replace surgical and fluid losses and maintain a volume-replete state. The left ureter was cannulated for urine collections, and the left kidney was immobilized for micropuncture by placing it in a stainless steel kidney cup. A 1.5- or 2.0-mm flow probe was placed around the left renal artery to allow for measurement of RBF using an electromagnetic flowmeter (Carolina Medical Electronics, King, NC). The left kidney was denervated by stripping all visible nerves from the renal artery, and the artery was coated with a 5% solution of phenol in ethanol. A micro-Blalock clamp was placed on the aorta above the renal arteries, and ligatures were placed around the superior mesenteric and celiac artery to allow for control of RPP. Circulating levels of vasopressin and norepinephrine were fixed at high levels by intravenous infusion (vasopressin, 2.4 U·ml^{-1}·min^{-1}; norepinephrine, 100 ng/min; obtained from Sigma, St. Louis, MO).

Protocol 1: Autoregulation of whole kidney, cortical, and medullary blood flow. After surgery and a 30-min equilibration period, the relationships between whole kidney, cortical, and papillary blood flow and RPP were determined. These studies were performed in volume-replete FHH and FHL rats prepared as described above and in other rats that were volume expanded by intravenous infusion of 6 ml of a 0.9% NaCl solution containing 6% BSA. The degree of volume expansion was similar in all rats. In each animal, systemic arterial pressure was first increased ~25 mmHg by tying off the celiac and mesenteric arteries. Then RBF and laser-Doppler red blood cell (RBC) flux signals obtained from the renal cortex and the inner medulla were recorded as RPP was varied from 150 to 50 mmHg in steps of 10 mmHg by tightening the clamp on the aorta above the renal arteries. The kidney was perfused at each RPP for 5 min or until steady-state blood flow signals were recorded.

RBF was measured using an electromagnetic flowmeter, and laser-Doppler RBC flux in the renal cortex was measured using a special large-diameter fiber-optic integrating probe (Pf 342) and a dual-channel laser-Doppler flowmeter (model Pf3; Perimed, Stockholm, Sweden). Medullary RBC flux was simultaneously measured using a second Pf3 laser-Doppler flowmeter and a F316 fiber-optic probe coupled to an optical fiber that was implanted at a depth of 5 mm in the kidney and secured in place using a drop of cyanoacrylic adhesive as previously described (21). The exact location of the implanted fiber at the junction of the outer and inner medulla was verified at the end of each experiment by dissecting the kidney and viewing the regions surrounding the tip of the fiber. To allow for comparisons of laser-Doppler flow signals between instruments, both laser-Doppler flowmeters were calibrated by placing the probes in a standard solution containing a colloidal suspension of 10-μm latex microspheres (Pf100; Perimed, Stockholm, Sweden) to read a flux value of 2.5 V, and the shifted light intensity was adjusted to read a normalized value of 7.75 V. This calibration is necessary for these instruments to produce a signal proportional to RBC flux rather than velocity alone.

Protocol 2: Micropuncture experiments. These experiments were performed in volume-replete FHH and FHL rats, which were surgically prepared as described above, and the left kidney was placed in a stainless steel kidney cup and surrounded with 2.5% agar (Sigma). The surface of the kidney was constantly bathed with warm (37°C) 0.9% NaCl solution. In each animal, RPP was adjusted to 100, 125, and 150 mmHg by adjusting the resistance of the clamp on the aorta, and hydrostatic pressures were measured in three to five peritubular capillaries, proximal tubules (proximal tubular pressure) and star vessels [efferent arteriolar pressure (P_E)] using a 7-μm-OD glass micropipette filled with 2 M NaCl containing fast green (Sigma). The pressures were measured using a model 900 servo-null micropressure system (World Precision Instruments, Sarasota, FL) and recorded using a polygraph (Grass Instruments, Quincy, MA). P_{GC} values were estimated in four to six different nephrons at each level of RPP using the proximal stop-flow technique. In these experiments, an early proximal tubule was blocked with Sudan-black stained bone wax (Ethicon, W31-G) using a 10- to 12-μm-OD micropipette connected to a hydraulic microdrive unit (Stoelting Instruments). The servo-null pressure-sensing pipette was then introduced upstream of the wax block, and the stop-flow hydrostatic pressure was measured.

Protocol 3: Isolated perfused vessels. Rats were anesthetized with a 50 mg/kg intraperitoneal injection of pentobarbital sodium, and the left kidney was rapidly removed and placed in ice-cold (4°C) bicarbonate-buffered physiological salt solution (PSS) containing (in mM): 144 Na$^+$, 124 Cl$^-$, 2.5 Ca^{2+}, 4.7 K$^+$, 1.2 Mg^{2+}, 1.2 PO$_4^{3-}$, 15 HCO$_3^-$, 11 glucose, 10 HEPES, and 0.026 EDTA at pH 7.4. The kidney was hemisected, and interlobular arteries (70–100 μm) were microdissected near the junction of the cortex and outer medulla using a stereomicroscope (×60). One vessel was isolated from the kidney of each animal. Arterial segments 8–10 mm in length were placed in a perfusion chamber, cannulated at both ends with glass pipettes, and secured in place with 10–0 silk suture (Ethicon). Side branches, when present, were tied off with the same suture. The arterial segments were perfused and superperfused with PSS at 37°C. The inflow cannula was connected in series with a pressure reservoir and a transducer (Spectramed, Oxnard, CA). During the measurements, the outflow cannula was clamped off to maintain a given level of transmural pressure as previously described (16, 20).

The internal diameter of the vessel was monitored using a television camera (model KP130; Hitachi, Denshi, Tokyo, Japan) and a stereomicroscope (model DRC; Zeiss, Oberkochen, Germany). The image was displayed on a monitor (model CVM-1271; Sony, Tokyo, Japan), and vessel diameters were measured using a video dimension analyzer (VIA-100; Boeckeler Instruments, Tucson, AZ). Magnification on the screen was approximately ×180, and the measurement system was calibrated with a micrometer to a diameter within ± 2.0 μm.

Cannulated rat renal interlobular arteries were maintained at 80 mmHg during a 30-min equilibration period. After an equilibration period of 30 min, the viability of each vessel was tested by constructing a cumulative dose-response curve to phenylephrine (PE) followed by ACh. Then a control myogenic response curve was constructed by measuring internal diameter of the vessels as transmural pressure was varied from 50 to 150 mmHg in steps of 10 mmHg. After this control relationship was determined, the bath was changed with Ca^{2+}-free PSS. After a 30-min equilibration period, the pressure-diameter curves were redetermined to obtain the passive properties of the vessel.

Glomerular morphology. After completion of each in vivo study, coronal sections of both kidneys were immersed in 3% Formalin. After fixation, 2- to 3-mm slices of renal tissue were embedded in paraffin and prepared for light microscopy. The

extent of glomerular damage was determined in 3-μm sections stained with periodic acid-Schiff reagent. In each animal, 50 glomeruli were scored for the presence of sclerotic lesions, mesangial matrix expansion, and adhesion formation between tuft and Bowman's capsule. The extent of glomerular damage is expressed as the percentage of the glomeruli exhibiting one or more of these features. The incidence of rats exhibiting the different types of renal damage was not assessed separately.

Calculations and statistics. Data are presented as mean values ± 1 SE. Whole kidney blood flow data were factored per gram of kidney weight. RBF autoregulatory indexes over the range of pressures from 100 to 140 (volume-replete) or 150 mmHg (volume-expanded) were calculated as the percentage change in the electromagnetic flow signal divided by the percentage change of RPP. The laser-Doppler flow data are presented as absolute RBF flux values in volts, and the autoregulatory indexes were calculated as described above.

Plasma protein concentrations were measured using a clinical refractometer (model N; Atago), and glomerular capillary oncotic pressure was assumed to equal the oncotic pressure of arterial blood. Plasma oncotic pressure was calculated from the plasma protein concentration using the Landis-Pappenheimer equation (19)

$$\pi = 0.0092 \ C^3 + 0.16 \ C^2 + 2.1 \ C$$

where C is concentration in units of grams per deciliter (valid over the range of 4–10 g/dl) and π is plasma oncotic pressure in millimeters mercury.

Active tension in the vascular wall was calculated from the measured active and passive vessel diameters using the following equation (22)

$$T_a (dyne/cm) = -1,333 (dyne/cm^2 \times mmHg)$$
$$\times P \times (R_a - R_p) \times 10^{-4} (cm/\mu m)$$

where T_a is the active wall tension, P is the transmural pressure in millimeters mercury, and R_a and R_p are the radii of the vessels in micrometers measured in PSS and calcium-free PSS. Vascular diameters are presented as percentages of the control diameter measured in each vessel when it was perfused and bathed with PSS at a transmural pressure of 70 mmHg (pressure at which these vessels exhibited a maximal diameter). The level of relaxation in response to increasing doses of ACh was calculated as percent of PE (10^{-5} M) preconstricted inner diameter. The inhibitory effect of PE is expressed as the change in diameter reduction in active tension measured in the vessels during the control period at a pressure of 80 mmHg.

Significance of differences in measured values was evaluated using a two-way ANOVA for repeated measures followed by Duncan's multiple range test. A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

RBF responses. Autoregulation of RBF was studied in both volume-replete FHH and FHL rats and after plasma volume was expanded in these animals to minimize the contribution of TGF to this response. The results in volume-replete rats are presented in Fig. 1*A*. Control mean arterial pressures (MAP) averaged 149 ± 4 and 131 ± 4 mmHg in FHH (*n* = 12) and FHL (*n* = 9) rats. Baseline RBF measured at these pressures was significantly greater in FHH than in FHL rats and averaged 9.3 ± 0.5 and 6.9 ± 0.3 ml·min⁻¹·g kidney
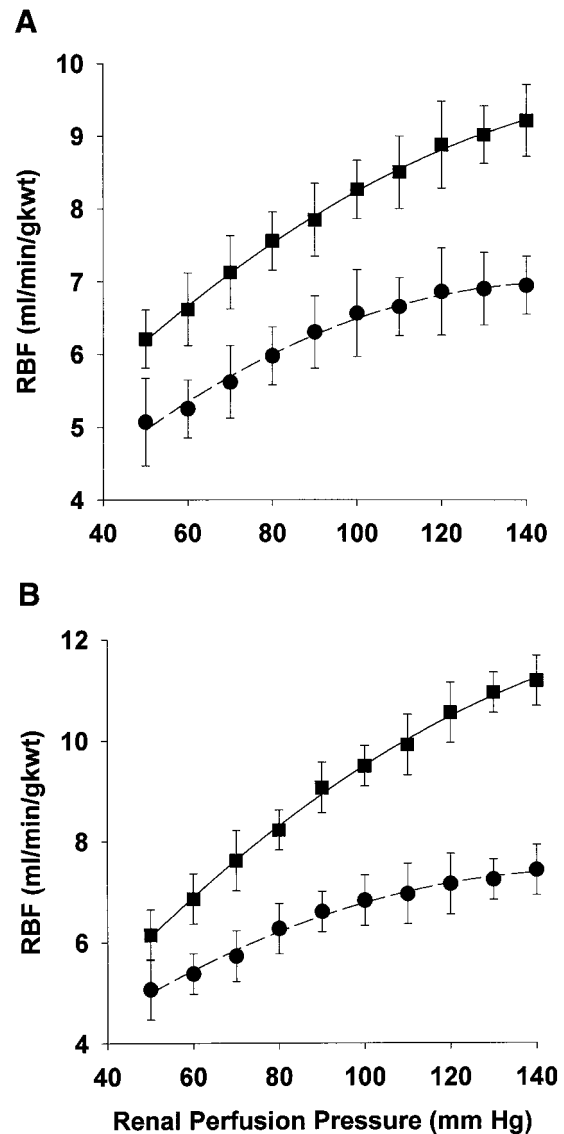

Fig. 1. *A* and *B*: relationship between renal perfusion pressure (RPP) and whole kidney renal blood flow (RBF) in ml·min⁻¹·g kidney wt⁻¹ in volume-replete (*A*) and volume-expanded (*B*) fawn-hooded hypertensive (FHH, ■, *n* = 12) and fawn-hooded low blood pressure (FHL, ●, *n* = 9) rats. Kidney weights averaged 2.50 ± 0.03 and 2.51 ± 0.06 g in FHH and FHL rats, respectively. Values are means ± SE. kwt, kidney wt.

wt⁻¹, respectively. RBF was autoregulated in both FHL and FHH rats over the range of pressures from 100 to 150 mmHg under these experimental conditions. However, autoregulation of RBF was less efficient in volume-replete FHH than in FHL rats. This is reflected in the autoregulatory indexes that were significantly different in volume-replete FHH and FHL rats and averaged 0.36 ± 0.12 vs. 0.19 ± 0.09, respectively. We also noted that the time course of the autoregulatory response differed in volume-replete FHH and FHL rats. Autoregulation of RBF was complete within 10 s after a fall in RPP in FHL rats, whereas the time course of the autoregulatory response was different in volume-replete FHH rats, and it generally took 3–4 min for RBF to return to control values after a fall in RPP.

A comparison of the relationships between RPP and whole kidney blood flow after plasma volume expansion in FHH and FHL rats is presented in Fig. 1B. Baseline MAP in these rats measured before abdominal surgery averaged 147 ± 3 ($n = 12$) and 132 ± 2 mmHg ($n = 9$). Baseline RBF increased significantly more in FHH than in FHL rats after volume expansion and averaged 11.2 ± 0.5 and 6.7 ± 0.9 ml·min^{-1}·g kidney wt^{-1}, respectively. RBF was not well autoregulated after plasma volume expansion in FHH rats, and the RBF autoregulatory index averaged 0.96 ± 0.12 over a range of RPPs from 100 to 150 mmHg. In contrast, FHL rats retained some ability to autoregulate RBF after plasma volume expansion, and the autoregulatory index averaged 0.42 ± 0.04.

The relationship between RPP and cortical blood flow measured by laser-Doppler flowmetry in volume-replete FHH and FHL rats is presented in Fig. 2A. Baseline MAP measured before abdominal surgery averaged 154 ± 3 and 129 ± 2 mmHg in volume-replete FHH ($n = 7$) and FHL ($n = 7$) rats, respectively. Baseline cortical blood flow under this condition was significantly higher in FHH than in FHL rats and averaged 3.20 ± 0.25 and 2.94 ± 0.05 V, respectively. Autoregulation of cortical blood flow was less efficient in volume-replete FHH compared with volume-replete FHL rats. Autoregulatory indexes over the pressure range of 100–140 mmHg in FHH and FHL rats averaged 0.30 ± 0.17 and 0.19 ± 0.06, respectively.

The relationship between RPP and medullary blood flow measured by laser-Doppler flowmetry in volume-replete FHH and FHL rats is presented in Fig. 2B. Autoregulation of blood flow was significantly less efficient in the medulla of FHH ($n = 7$) compared with FHL rats ($n = 7$), with indexes over the pressure range of 100–140 mmHg of 0.78 ± 0.29 and 0.37 ± 0.23, respectively.

The relationship between RPP and cortical blood flow in the volume-expanded state is shown in Fig. 3A. Somewhat higher perfusion pressures could be obtained in the volume-expanded compared with the volume-replete state. Blood flow over the pressure range of 100–150 mmHg was not efficiently autoregulated under this condition in FHH rats ($n = 7$), with an index of 0.86 ± 0.30. In contrast, blood flow in the cortex of volume-expanded FHL rats ($n = 5$) was more efficiently autoregulated, with an index of 0.37 ± 0.20.

Baseline medullary blood flow after acute volume expansion, shown in Fig. 3B, was significantly higher in FHH than in FHL rats and averaged 1.71 ± 0.04 and 1.24 ± 0.32 V, respectively. Medullary blood flow was less efficiently autoregulated in volume-expanded FHH rats ($n = 7$) than in FHL rats ($n = 5$), with indexes over the pressure range of 100–150 mmHg of 1.06 ± 0.26 and 0.72 ± 0.20, respectively.

Micropuncture experiments. A comparison of pressures measured in proximal tubules, star vessels (efferent arterioles), and P_{GC} estimated from proximal tubule stop flow pressures in FHH and FHL rats is presented in Figs. 4 and 5. Control MAP averaged 159 ± 4 mmHg ($n = 9$) in FHH and 130 ± 2 mmHg ($n = 6$) in FHL rats.
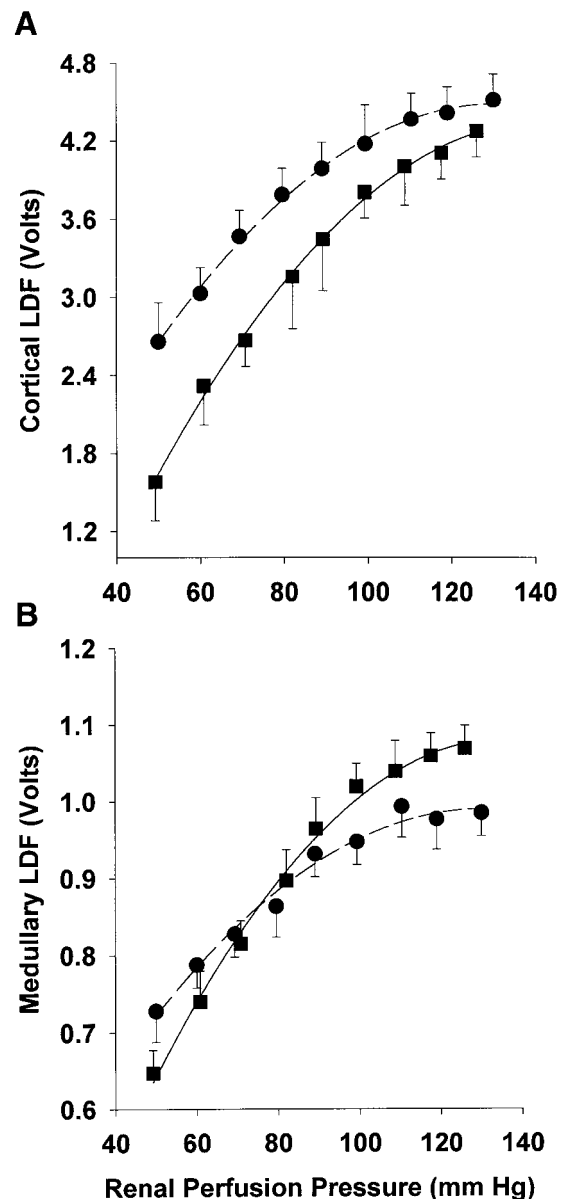

Fig. 2. *A* and *B*: relationship between RPP and cortical (*A*) and medullary laser-Doppler flux (LDF) (*B*) in volume-replete FHH (■, $n = 7$) and FHL (●, $n = 7$) rats. Values are means ± SE.

Pressures measured in proximal tubules (Fig. 4A) were similar and averaged 22 ± 2, 23 ± 2, and 24 ± 2 mmHg in FHH and 19 ± 2, 20 ± 2, and 21 ± 2 mmHg in FHL rats at an RPP of 100, 125, and 150 mmHg, respectively. P_E (Fig. 4B) at an RPP of 100 and 125 mmHg averaged 23 ± 2 and 25 ± 2 mmHg in FHH and 22 ± 2 and 23 ± 2 mmHg in FHL rats, respectively. At a higher RPP of 150 mmHg, P_E was not autoregulated and rose to 34 ± 1 mmHg in FHH rats. This value was significantly higher than the corresponding value measured in FHL rats (24 ± 2 mmHg). In FHH rats, P_{GC} (Fig. 5) increased dramatically as RPP was elevated and averaged 46 ± 1 mmHg at an RPP of 100 mmHg, 58 ± 2 mmHg at an RPP of 125 mmHg, and 71 ± 1 mmHg at an RPP of 150 mmHg. The rise in P_{GC} with an increase in RPP was less dramatic in FHL rats and averaged
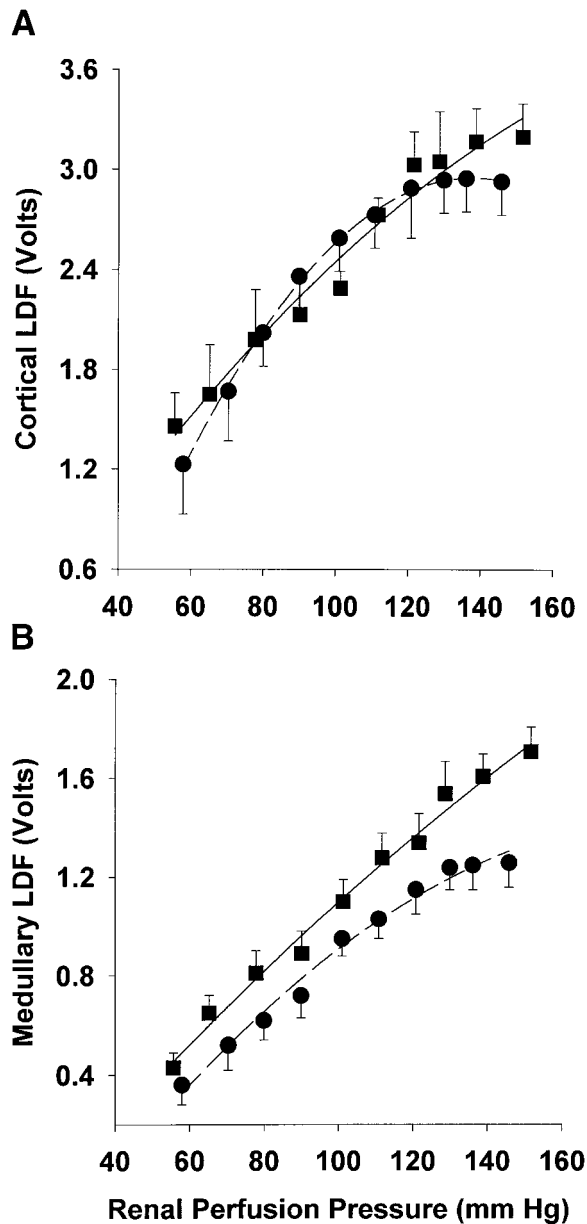
A

B

Fig. 3. *A* and *B*: relationship between RPP and cortical (*A*) and medullary LDF (*B*) in volume-expanded FHH (●, *n* = 7), and FHL (■, *n* = 5) rats. Values are means ± SE.

2.1% of control in response to an elevation in transmural pressure from 70 to 120 mmHg. After removal of calcium from the bath, the diameter of these vessels increased as the transmural pressure was varied over this same range. In contrast, renal interlobular arteries obtained from the kidneys of FHH rats did not constrict in response to an elevation in transmural pressure. Rather, diameter of these vessels increased significantly to 113.1 ± 1.7% of control when pressure was elevated from 70 to 120 mmHg.

The increase in vessel diameter with no calcium in the bath was similar in FHH and FHL vessels, although values were numerically higher in FHH compared with FHL. This might indicate that the inner diameter from vessels from FHH rats increase more in response to an increase in transmural pressure and therefore dilate more in response to increases in transmural pressure in the absence of calcium than vessels from FHL rats.
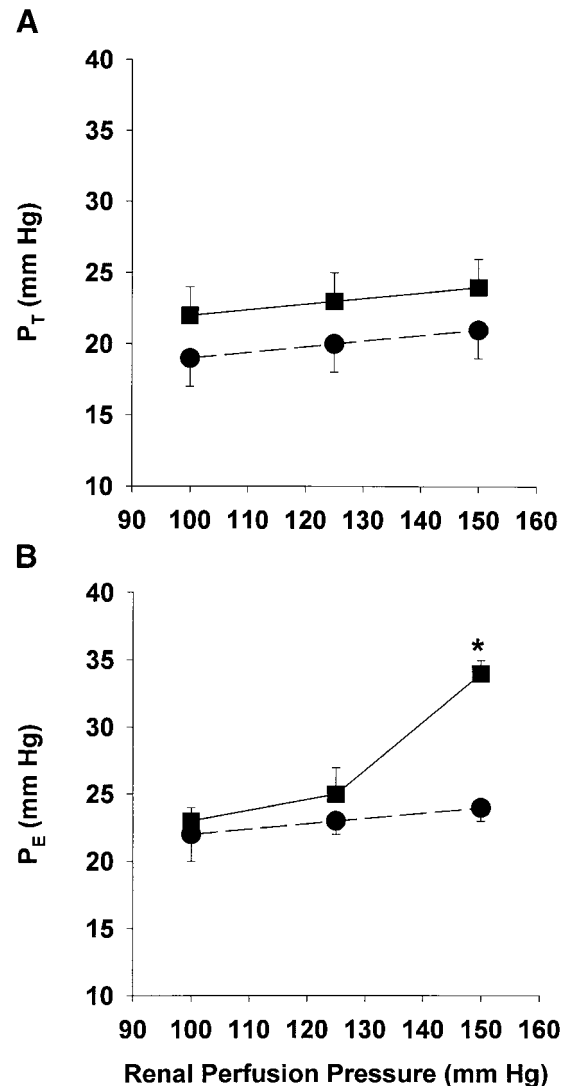
A

B

Fig. 4. *A* and *B*: relationship between RPP, proximal tubular pressure (P_T; *A*) in mmHg, and efferent arteriolar pressure (P_E; *B*) in mmHg in FHH (■, *n* = 9) and FHL (●, *n* = 6). Values are means ± SE. *$P < 0.05$, FHH compared with FHL.

39 ± 1, 47 ± 2, and 53 ± 1 mmHg at an RPP of 100, 125, and 150 mmHg, respectively. The relative change in P_{GC} as a function of the relative change in RPP (P_{GC} autoregulatory index) averaged 0.78 ± 0.11 in FHL versus 1.06 ± 0.23 in FHH rats and showed better preservation of P_{GC} in FHL compared with FHH rats.

Myogenic response of renal interlobular arteries. The pressure-diameter relationships in renal interlobular arteries of FHH (*n* = 5) and FHL (*n* = 5) rats are presented in Fig. 6*A*. The baseline diameters of interlobular arteries of FHH and FHL rats at a transmural pressure of 70 mmHg were not significantly different and averaged 99.6 ± 24.3 and 109.5 ± 13.6 μm, respectively. Vessels obtained from the kidneys of FHL rats exhibited a typical myogenic response, and the inner diameter of these vessels decreased to $92.2 \pm$
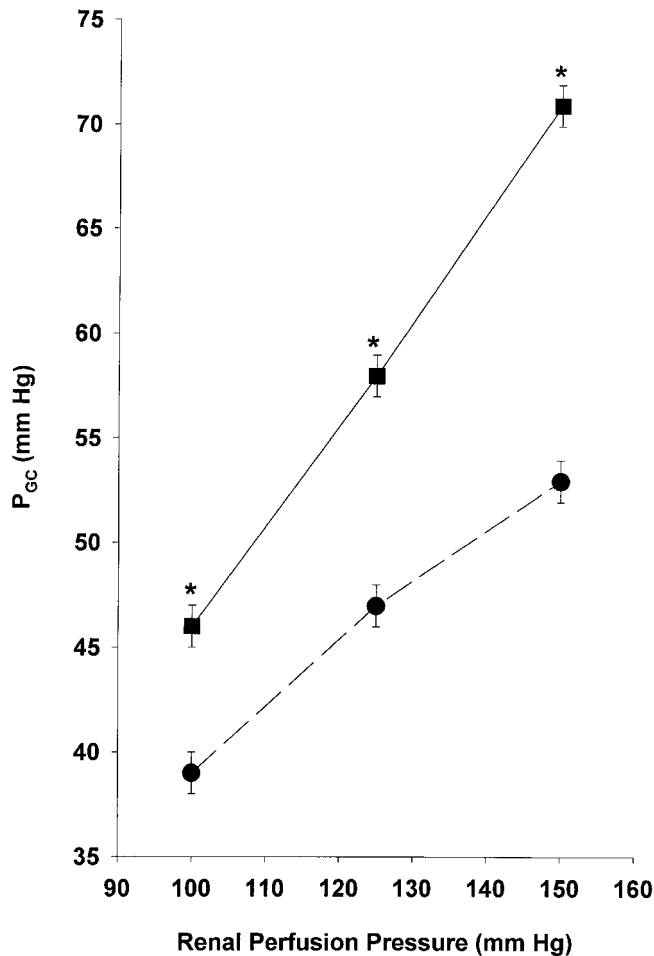
Fig. 5. Relationship between RPP in mmHg and glomerular capillary pressure (P_{GC}) in mmHg in FHH (■, $n = 9$) and FHL (●, $n = 6$) rats. Values are means ± SE. * $P < 0.05$, FHH compared with FHL.

A comparison of the relationship between the percentage change in active wall tension and transmural pressure in vessels obtained from the kidneys of FHH and FHL rats is presented in Fig. 6B. Active wall tension rose from 78 to 597% of active tension at 80 mmHg in response to an increase in transmural pressure from 70 to 120 mmHg in vessels obtained from the kidneys of FHL rats. In contrast, vessels obtained from the kidneys of FHH rats ($n = 5$) failed to respond, and active tension did not increase significantly as pressure was increased over this same range.

To exclude the possibility that the failure of FHH vessels to respond to elevations in transmural pressure was not due to nonspecific vascular injury, the vasoconstrictor responses of FHH and FHL rat vessels to PE were compared. The results of these experiments are presented in Fig. 7A. Vessels from the kidneys of FHH and FHL rats constricted similarly to increasing doses of PE. The only significant difference in the dose-response curve was a slightly diminished response in vessels from FHH kidneys at a concentration of 10^{-7} M.

The responses of FHH and FHL renal interlobular arteries to ACh were also compared because endothelial dysfunction has been reported to be a common finding in many experimental and genetic models of

hypertension. The results of these experiments are presented in Fig. 7B. Acetylcholine increased the diameter of interlobular arteries obtained from the kidneys of FHL rats in a dose-dependent manner to 80% of control. In contrast, vessels obtained from the kidneys of FHH rats did not respond to even relatively high concentrations of ACh (10^{-6} M).

Glomerular injury. Total kidney weight was not significantly different in FHH and FHL rats and averaged 2.50 ± 0.03 and 2.51 ± 0.06 g, respectively. The incidence of glomerulosclerosis in the kidneys of these 3-mo-old FHH and FHL rats was not significantly different. Only 1.6 ± 0.6% of the glomeruli exhibited any signs of glomerulosclerosis in the kidneys of FHH
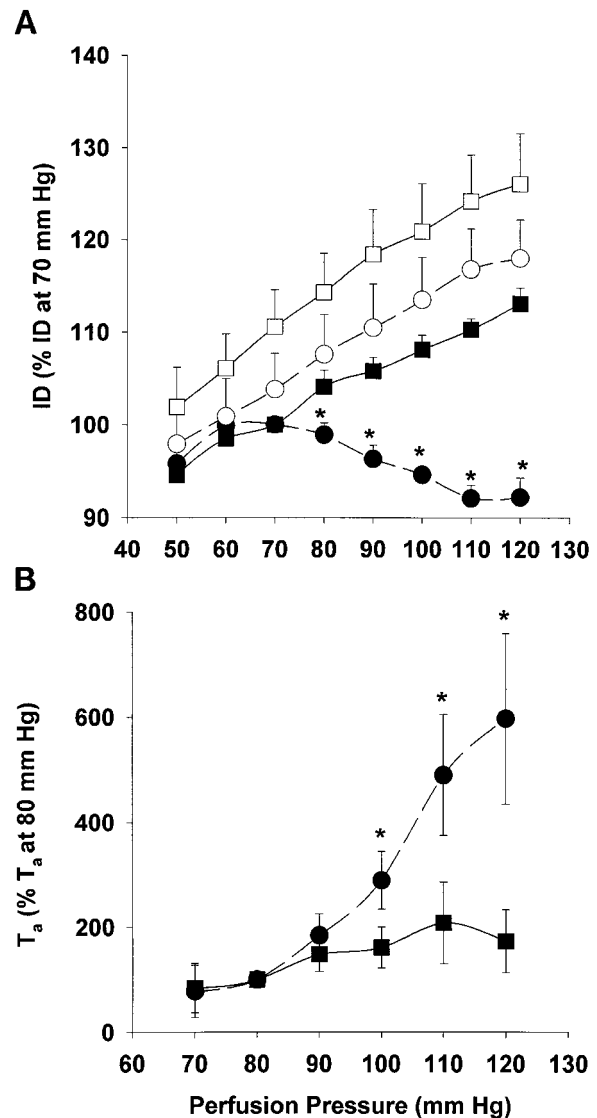

Fig. 6. *A*: relationship between perfusion pressure in mmHg and inner diameter (ID) of interlobular arteries in %ID at 70 mmHg in calcium-containing (closed symbols) and calcium-free (open symbols) medium in interlobular arteries of FHH (■ and □, $n = 5$) and FHL (● and ○, $n = 5$) rats. *B*: relationship between perfusion pressure in mmHg and pressure-active tension (T_a) in %T_a at 80 mmHg in interlobular arteries of FHH (■, $n = 5$) and FHL (●, $n = 5$) rats. Values are means ± SE. * $P < 0.05$, FHL compared with FHH.
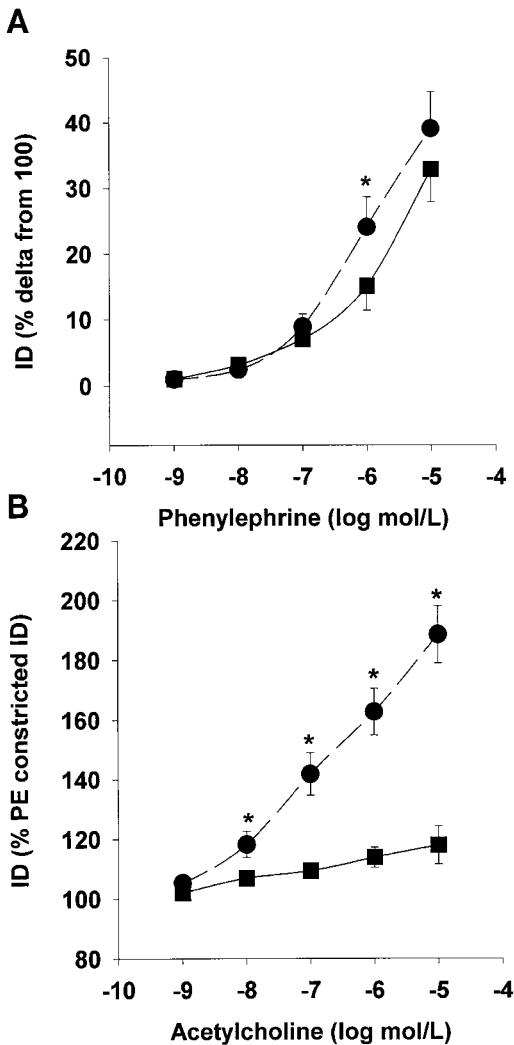
Fig. 7. *A*: relationship between responses to increasing doses of phenylephrine (PE) in log mol/l and ID in %change (delta) from 100 in interlobular arteries of FHH (■, *n* = 5) and FHL (●, *n* = 5) rats. * *P* < 0.05, FHL compared with FHH. *B*: relationship between responses to increasing doses of ACh in log mol/l and ID expressed as %PE (10^{-5} M) constricted ID in interlobular arteries of FHH (■, *n* = 5) and FHL (●, *n* = 5) rats. Values are means ± SE. * *P* < 0.05, FHH compared with FHL.

rats versus an incidence of $1.2 \pm 0.4\%$ observed in the kidneys of FHL rats.

DISCUSSION

The present study compared changes in RBF and cortical and medullary blood flow in response to alterations in RPP in the kidneys of FHL and FHH rats to determine whether an impairment in the myogenic component of renal autoregulation might contribute to the development of glomerular disease in FHH rats. We found that baseline RBF was significantly greater in volume-replete FHH than in FHL rats. Under this experimental condition, both FHH and FHL rats autoregulated RBF. However, the efficiency of autoregulation was slightly but significantly greater in FHL than in FHH rats. The most striking difference seen was in the time course of the response. Autoregulatory adjust-

ments in renal vascular resistance were complete within seconds in FHL after a reduction in RPP, whereas it typically took more than 3–4 min for RBF to return to control in FHH rats. This finding suggests that the rapid myogenic component of autoregulation may be impaired in FHH rats but that the TGF component of renal autoregulation, which exhibits a much longer time constant, is still intact. This view is also consistent with the recent findings of Verseput et al. (28), who found an intact TGF response in FHH rats studied at about the same age as those used in the present study.

This hypothesis is further supported by the results of experiments performed in volume-expanded FHH and FHL rats to minimize the contribution of TGF to autoregulation of RBF (15). Baseline whole kidney, cortical, and medullary blood flows were markedly elevated in volume-expanded FHH rats. Under these conditions, FHH rats did not autoregulate whole kidney, cortical, or medullary blood flow as efficiently as FHL rats. Overall, these results suggest that the myogenic response of the preglomerular vasculature to changes in transmural pressure is markedly impaired in FHH rats.

Micropuncture experiments were performed to further evaluate this hypothesis. P_{GC} was estimated from proximal tubule stop flow pressures and compared in volume-replete FHH and FHL rats at different levels of RPP. Under these conditions, flow to the macula densa is interrupted and the contribution of TGF to the autoregulation of P_{GC} is eliminated. Our results indicate that volume-expanded FHL rats retain some ability to autoregulate P_{GC} via activation of myogenic mechanisms but FHH rats do not. Indeed the percentage change in P_{GC} as a function of RPP (P_{GC} autoregulatory index) averaged 0.78 in FHL versus 1.06 in FHH rats. Another interesting observation is that although P_{GC} was not autoregulated and markedly elevated in FHH rats, there was little difference in the relationship between pressures in the peritubular capillaries and RPP in FHH and FHL rats. This implies that the resistance of the efferent arteriole must increase in FHH because RPP was elevated. This may be related to some capacity of the efferent arteriole to respond actively to elevations in P_{GC} or some unknown mechanism that remains to be explored.

Finally, the hypothesis that the myogenic response of the preglomerular vasculature is altered in FHH rats was directly tested using isolated perfused renal interlobular arteries. The results of these studies indicate that vessels obtained from FHL rats constricted and active wall tension increased in response to an elevation in transmural pressure, whereas vessels obtained from FHH rats failed to exhibit a myogenic response. Indeed, the diameter of these vessels increased in response to an elevation in transmural pressure, and there was no significant difference in the pressure-diameter curve in these vessels studied in the presence and absence of calcium in the bath. These isolated vessel data further support the micropuncture data and indicate that an impairment in the myogenic response of the preglomerular vasculature of FHH rats

contributes to the lack of autoregulation of RBF and P_{GC} in these animals, especially after acute volume expansion. However, impairment of the myogenic responses in interlobular arteries alone would not have much impact on autoregulation of RBF or P_{GC} because most of the preglomerular pressure drop in the rat occurs along the afferent arteriole. For this reason, we believe that myogenic response must be impaired throughout the preglomerular renal vasculature and particularly in the afferent arteriole in the kidney of the FHH rat.

The inability of renal interlobular arteries from FHH rats to respond to elevations in transmural pressure was not due to nonspecific vascular damage, because they exhibited a normal vasoconstrictor response to PE. We did, however, find that the vasodilator response to acetylcholine was blunted in FHH rats. The importance of this observation remains to be determined, but it is consistent with a large body of emerging evidence indicating that hypertension is often associated with endothelial dysfunction (5, 7, 8, 20, 24).

Perspectives

The results of the present study indicate that the myogenic response of preglomerular renal arteries is impaired in FHH rats, and they exhibit an impaired ability to buffer changes in intraglomerular pressure, especially in response to rapid fluctuations in arterial pressure. This defect in the myogenic response of the preglomerular vasculature, in combination with the previously reported increased efferent vascular resistance that elevated baseline P_{GC} (25, 26), and the tendency of these animals to develop systolic hypertension promote the transmission of elevated pressures to the glomerulus. Because elevations in P_{GC} have been previously linked to the development of glomerulosclerosis in many different experimental models of renal disease (2, 14, 26), it is likely that this also contributes to the development of proteinuria and renal disease in FHH rats as well and probably greatly depends on the genetic susceptibility of this rat strain to develop renal damage (4, 12, 13).

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