Impaired autoregulation of renal blood flow in the fawn-hooded rat

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Van Dokkum, Richard P. E., Magdalena Alonso-Galicia, Abraham P. Provoost, Howard J. J. Jacob, and Richard J. Roman. Impaired autoregulation of renal blood flow in the fawn-hooded rat. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R189–R196, 1999.—The responses to changes in renal perfusion pressure (RPP) were compared in 12-wk-old fawn-hooded hypertensive (FHH), fawn-hooded low blood pressure (FHL), and August Copenhagen Irish (ACI) rats to determine whether autoregulation of renal blood flow (RBF) is altered in the FHH rat. Mean arterial pressure was significantly higher in conscious, chronically instrumented FHH rats than in FHL rats (121 ± 4 vs. 109 ± 6 mmHg). Baseline arterial pressures measured in ketamine-Inactin-anesthetized rats averaged 147 ± 2 mmHg (n = 9) in FHH, 132 ± 2 mmHg (n = 10) in FHL, and 123 ± 4 mmHg (n = 9) in ACI rats. Baseline RBF was significantly higher in FHH than in FHL and ACI rats and averaged 9.6 ± 0.7, 7.4 ± 0.5, and 7.8 ± 0.9 ml·min⁻¹·g kidney wt⁻¹, respectively. RBF was autoregulated in ACI and FHL but not in FHH rats. Autoregulatory indexes in the range of RPPs from 100 to 150 mmHg averaged 0.96 ± 0.12 in FHH vs. 0.42 ± 0.04 in FHL and 0.30 ± 0.02 in ACI rats. Glomerular filtration rate was 20–30% higher in FHH than in FHL and ACI rats. Elevations in RPP from 100 to 150 mmHg increased urinary protein excretion in FHH rats from 27 ± 2 to 87 ± 3 µg/min, whereas it was not significantly altered in FHL or ACI rats. The percentage of glomeruli exhibiting histological evidence of injury was not significantly different in the three strains of rats. These results indicate that autoregulation of RBF is impaired in FHH rats before the development of glomerulosclerosis and suggest that an abnormality in the control of renal vascular resistance may contribute to the development of proteinuria and renal failure in this strain of rats.

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METHODS

General. Experiments were performed on 52 male FHH, FHL, and ACI rats. The rats were studied at 12 wk of age, when there is no functional and structural evidence of renal damage in any of these strains. Body weights averaged 263 ± 29, 260 ± 21, and 194 ± 8 g in FHH, FHL, and ACI rats, respectively. The FHH and FHL rats were obtained from colonies maintained at the Medical College of Wisconsin that were derived from the original colony maintained by Dr. Provoost at the Erasmus University in Rotterdam (FHH/EUR and FHL/EUR). ACI rats were purchased from Harlan Sprague Dawley Laboratories (Indianapolis, IN). The rats were housed in an animal care facility at the Medical College of Wisconsin, which is approved by the American Association for the Accreditation of Laboratory Animal Care, and had free access to food and water throughout the study. The day before the acute experiments were performed, food was withdrawn overnight to facilitate surgical procedures. Acute studies of renal function. Rats were anesthetized with a 10 mg/kg im injection of ketamine (Ketajet; Phoenix...
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Scientific, St. Joseph, MO) and a 30 mg/kg ip injection of 5-sec-butyl-5-ethyl-2-thioibarbituric acid (Inactin; Byk-Gulden, Konstanz, Germany). The animals were placed on a thermostatically controlled warming table to maintain body temperature at 37°C. A PE-50 cannula was placed in the femoral artery, and arterial pressure was recorded with a model P23 Gould Statham pressure transducer (Gould, Cleveland, OH) connected to a model RPS 788 Grass amplifier (Grass Instruments, Quincy, MA). A PE-50 cannula was placed in the left carotid artery to allow for measurement of arterial pressure when the aorta below the renal arteries was ligated to raise renal perfusion pressure (RPP). The trachea was cannulated with PE-240 tubing to facilitate breathing. A catheter was also placed in the left external jugular vein, and the rat received an intravenous infusion of 1% bovine serum albumin in a 0.9% NaCl solution at a rate of 100 µl/min throughout the experiment. Both ureters were cannulated using PE-50 tubing pulled to a tip diameter of 200 µm for timed urine collections. A 1.5- or 2.0-mm flow probe was placed around the left renal artery to measure RBF using an electromagnetic flowmeter (Carolina Medical Electronics, King, NC). A micro-Bloack clamp (Medical College of Wisconsin, Milwaukee, WI) was placed on the aorta above the renal arteries, and ligatures were placed around the superior mesenteric and celiac arteries to allow for manipulation of RPP.

Neural and hormonal influences on the kidney were controlled as follows. The kidney was denervated by stripping the visible renal nerves and by coating the renal artery with a 5% solution of phenol in ethanol. Circulating levels of vasoprespin and norepinephrine were fixed at high levels by intravenous infusion (vasoprespin: 2.4 U·ml⁻¹·min⁻¹; norepinephrine: 100 ng/min). [³H]Julinin (2 µCi/ml) was also included in the infusion solution to allow for the measurement of GFR.

Experimental protocol. After surgery, 30 min were allowed for stabilization of urine flow and arterial pressure, and RPP was lowered to 100 mmHg by tightening the aortic clamp above the renal arteries. After a 20-min equilibration period, urine and plasma samples were collected during a 20-min clearance period. The aortic clamp was then released to allow RPP to return to 120 mmHg, and urine and plasma samples were collected during an additional 20-min clearance period. RPP was then decreased to 150 mmHg by tightening the ligatures around the superior mesenteric and celiac arteries and by tightening the clamp on the lower aorta below the renal arteries when necessary. After a 10-min equilibration period, urine and blood samples were collected during a 20-min clearance period. In most, but not all, rats an RBF autoregulatory curve was generated after the pressure diuresis experiment. However, this experiment could not be completed in every rat because RPP often could not be maintained at a high enough level because fawn-hooded rats have a bleeding disorder. Therefore, additional rats had to be included in the blood flow autoregulation studies only to obtain enough animals for adequate statistics.

In these experiments, the renal artery was briefly occluded distal to the flow probe to obtain a zero-flow signal. RBF was then continuously recorded as RPP was lowered from 150 to 50 mmHg in steps of 10–20 mmHg. The kidney was perfused at each pressure step for 3 min until a steady-state level of RBF was recorded.

Measurement of arterial pressure in conscious rats. Arterial pressure was measured in conscious 12-wk-old FHH (n = 5) and FHL (n = 5) rats fed a normal (1% NaCl) diet. Studies were also performed in a group of 36-wk-old FHH rats (n = 5) that had advanced glomerulosclerosis. The rats were anesthetized with ketamine, xylazine, and acepromazine (50, 3.2, and 0.8 mg/kg im), and a catheter (MRE-025/Tygon) was implanted in the femoral artery. The catheter was routed subcutaneously to the scapular region, exteriorized through a Dacron mesh button (Instech), and protected with a stainless steel spring that also served to tether the rats to a swivel. After surgery, the rats were housed in individual cages in a quiet, air-conditioned room with a 12:12-h light-dark cycle and were allowed 1 wk to fully recover from surgery. The catheter was flushed daily with 0.2 ml of heparinized saline solution (100 USP/ml).

Mean arterial pressure (MAP) and heart rate (HR) were measured for 24 h on 3–4 consecutive days. Pulsatile arterial pressure signals were amplified, digitized, and analyzed with a computerized Apollo software system. The analog signal was sampled at 30 Hz, and the minute averages were used for calculation of daily MAP, SBP, diastolic blood pressure (DBP), and HR.

Analytic techniques. [³H]Julinin concentrations of urine and plasma samples were determined using a liquid scintillation counter (Delta 300 model 6891 Liquid Scintillation System; Tracor Analytic, Elk Grove Village, IL). Urine flow rate was determined gravimetrically. Sodium and potassium concentrations of the samples were determined using a flame photometer (model 480; Ciba Corning Diagnostics, Medfield, MA). Plasma and urine protein concentrations were measured spectrophotometrically using the Bradford method (Bio-Rad Protein Assay; Bio-Rad Laboratories, Hercules, CA) and bovine serum albumin as a standard. GFR and sodium excretion were calculated using standard formulas described previously (21, 22). Urinary excretion data, RBF, and GFR were factored per gram kidney weight to normalize for strain differences in kidney size. RBF autoregulatory indexes over the range of pressures from 100 to 150 mmHg were calculated by the method of Semple and de Wardener (23) using the following formula: RBF autoregulatory index = [(RBP₂ − RBP₁)/RBF₁] / [(RPP₂ − RPP₁)/RPP₁].

The autoregulatory indexes were calculated assuming that RPP was reduced in a single step from a high pressure (RPP₁) to a lower pressure (RPP₂). According to this analysis, an autoregulatory index of 0 indicates perfect autoregulation of RBF. An index of 1 is characteristic of a circulation with a fixed vascular resistance. An autoregulatory index >1 is indicative of a compliant system in which vascular resistance decreases as RPP increases (23).

Assessment of glomerular injury. At the end of each study, both kidneys were collected and weighed. A coronal section of the kidneys was immersed in 3% Formalin. After fixation, 2- to 3-mm slices of the 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, 100 glomeruli were evaluated for the presence of sclerotic lesions, i.e., segmental glomerular scarring, obliteration of glomerular capillaries, 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.

Statistical analysis. The significances of differences in mean values measured at different perfusion pressures between and within groups were compared using a two-factor ANOVA for repeated measures followed by Duncan’s multiple-range test (11). Linear regression analysis was used to calculate the relationship between urine flow, sodium excretion, and RPP in each group. Differences in the slopes of these relationships were compared using a one-way ANOVA. Throughout the study, a P value <0.05 was considered significant.
RESULTS

Autoregulation of RBF. A comparison of the RBF autoregulatory curves for FHH, FHL, and ACI rats is presented in Fig. 1A. Baseline MAP measured under ketamine-Inactin anesthesia was significantly higher in these animals than those measured in conscious FHH and FHL rats and averaged 147 ± 3 mmHg (n = 9) in FHH rats, 132 ± 2 mmHg (n = 10) in FHL rats, and 123 ± 4 mmHg (n = 9) in ACI rats. Baseline RBF was 35% higher in FHH rats compared with FHL and ACI rats (Fig. 1A). There was no significant difference in RBF between FHL and ACI rats. RBF was autoregulated over a range of pressures from 100 to 150 mmHg in FHL and ACI rats. Autoregulatory indexes over the pressure range between 100 and 150 mmHg averaged 0.42 ± 0.04 in FHL and 0.30 ± 0.02 in ACI rats. In contrast, RBF was not autoregulated in FHH rats. The autoregulatory index averaged 0.96 ± 0.12 in FHH rats, and it was significantly higher than the corresponding values measured in FHL and ACI. A similar picture emerges when the data are evaluated in 25-mmHg pressure steps (Fig. 1B). Below an RPP of 100 mmHg, none of the three strains exhibited any autoregulation of RBF (autoregulatory indexes were ~1). However, in the range of RPP from 100 to 125 and 125 to 150 mmHg, the RBF autoregulatory index in the FHH rats was significantly greater than that seen in FHL and ACI rats.

Pressure diuretic and natriuretic responses. The relations between water and sodium excretion and RPP in FHH, FHL, and ACI rats are summarized in Fig. 2, A and B, respectively. The diuretic and natriuretic responses to changes in RPP were not significantly
different among the strains. Urine flow and sodium excretion increased 6- to 12-fold in these rats when RPP was increased from 100 to 150 mmHg. The slopes of the best-fit linear regression lines relating urine flow and RPP averaged 0.85 ± 0.32, 0.79 ± 0.10, and 0.56 ± 0.12 ml·min⁻¹·g kidney wt⁻¹·mmHg⁻¹ in FHH, FHL, and ACI rats, respectively. The slopes of these lines were not significantly different. The slopes of the regression line relating sodium excretion and RPP were also not significantly different among the strains and averaged 0.13 ± 0.06, 0.12 ± 0.03, and 0.10 ± 0.05 mmol·min⁻¹·g kidney wt⁻¹·mmHg⁻¹ in FHH, FHL, and ACI rats, respectively. The pressure diuretic and natriuretic responses in the 36-wk-old FHH rats with advanced glomerular disease were markedly attenuated compared with those seen in the younger animals. The slope of the regression line relating sodium excretion and RPP in old FHH rats was significantly lower than those observed in the other three groups and averaged only 0.014 ± 0.002 mmol·min⁻¹·g kidney wt⁻¹·mmHg⁻¹ (not shown).

Elevating RPP from 100 to 150 mmHg increased fractional sodium excretion similarly from 0.6 ± 0.1 to 2.6 ± 0.5% and from 0.5 ± 0.08 to 3.1 ± 0.8% of the filtered sodium load in FHH and FHL rats, respectively (Fig. 3). These responses were significantly less than the corresponding response seen in ACI rats. In old FHH rats, the rise in fractional excretion of sodium was markedly blunted when RPP was elevated from 100 to 150 mmHg and it only increased from 0.38 ± 0.13 to 1.41 ± 0.37% of the filtered load (not shown). Moreover, fractional excretion of sodium was reduced in old and young FHH and FHL rats compared with values in ACI rats at an elevated level of RPP (150 mmHg).

Whole kidney GFR was significantly higher in young FHH than in FHL and ACI at every RPP studied and reached 2.37 ± 0.10 ml·min⁻¹·g kidney wt⁻¹ at an RPP of 150 mmHg (Fig. 4A). GFR was also greater in FHL than in ACI rats at an RPP of 125 mmHg and averaged 1.23 ± 0.03 vs. 0.56 ± 0.07 ml·min⁻¹·g kidney wt⁻¹, respectively. In old FHH rats, GFR was markedly reduced compared with values seen in all three groups of young animals. Similarly, RBF was lower in old FHH rats than the corresponding values observed in the other groups (not shown). The GFR autoregulatory indexes (Fig. 5A) showed no significant differences between the three strains between in the pressure range of 100 and 125 mmHg, whereas these indexes were significantly higher in FHH and ACI rats compared with FHL rats. The RBF autoregulatory indexes

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Fig. 3. Relationship between fractional sodium excretion (FE_{Na}) in percentage of filtered load and RPP in FHH (n = 9), FHL (n = 10), and ACI (n = 9) rats. Values are means ± SE.

Fig. 4. Relationships between glomerular filtration rate (GFR; A) and RBF (B) and RPP in FHH (n = 9), FHL (n = 10), and ACI (n = 9) rats. Kidney weights averaged 2.50 ± 0.03 g in FHH, 2.51 ± 0.06 g in FHL, and 1.92 ± 0.02 g in ACI rats. Values are means ± SE. All differences were statistically significant, except for RBF differences at 125 mmHg between FHL and ACI.
during the pressure natriuresis study (Fig. 5B) show similar values as in the autoregulatory studies between RPPs of 125 and 150 mmHg.

Pressure proteinuric responses. A comparison of urinary protein excretion as a function of RPP in FHH, FHL, and ACI rats is presented in Fig. 6. Basal protein excretion at a RPP of 100 mmHg was greater in FHH than in FHL and ACI, and averaged 27 ± 2, 16 ± 2, and 11 ± 1 µg/min, respectively. An elevation of RPP to 150 mmHg increased protein excretion to 87 ± 3 µg/min in FHH, whereas protein excretion was not significantly altered in FHL and ACI rats.

Measurement of arterial pressure. MAPs measured in conscious 12-wk-old FHH rats were slightly but significantly higher than those obtained in FHL rats. A period of between 6 and 48 h was used for analysis. In FHH rats (n = 5) the values for MAP, SBP, and DBP were 121 ± 4, 153 ± 3, and 98 ± 6 mmHg vs. 109 ± 6, 141 ± 6, and 89 ± 6 mmHg measured in FHL rats, respectively (n = 5). Mean pulse pressures averaged 55 ± 7 mmHg in FHH and 54 ± 3 mmHg in FHL rats; mean heart rate averaged 411 ± 25 beats/min in FHH and 436 ± 17 beats/min in FHL rats, and they were not significantly different. In 36-wk-old FHH rats, MAP was not significantly different from that measured in the younger FHH rats. However, MAP rose in the old FHH rats from 125 ± 4 to 142 ± 4 mmHg (n = 4) when they were fed a high-salt diet (8% NaCl) for 7 days.

Assessment of glomerular injury. Kidney weights were similar in FHH and FHL rats (2.50 ± 0.03 vs. 2.51 ± 0.06 g), and both were higher than those seen in ACI rats (1.92 ± 0.02 g). The percentages of glomeruli exhibiting any signs of injury were not significantly different in the three strains and averaged 1.8 ± 0.5% in FHH, 1.1 ± 0.5% in FHL, and 0.9 ± 0.6% in ACI rats. This indicates that the rats in these groups were studied at an age before the development of significant glomerular injury. In contrast, the kidneys of 36-wk-old FHH rats exhibited severe glomerulosclerosis and the percentage of injured glomeruli averaged 66 ± 8%.

DISCUSSION

The present study compared renal hemodynamics and the pressure natriuretic responses in relatively young (12 wk old) FHH with FHL and ACI rats to determine whether an abnormality in the autoregulation of RBF might precede the development of proteinuria and glomerular damage in the FHH rat. Our major findings are that RBF and GFR are markedly elevated in FHH rats compared with values observed in FHL rats.
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and ACI rats and that FHH rats do not autoregulate RBF as well as the control strains in the range of pressures from 100 to 150 mmHg. Indeed, the RBF autoregulatory index in FHH rats was significantly higher than those measured in both of the control strains and averaged 0.96 ± 0.12, which is indicative of a system with a fixed vascular resistance (23). These results are consistent with previous reports indicating that GFR and \( P_{GC} \) are elevated in the kidney of FHH rats and indicate that these animals probably exhibit a failure of the afferent arteriole to constrict in response to elevations in RPP (6, 25). Presumably this could involve an abnormality in myogenic mechanisms, tubuloglomerular feedback, or both. Because tubuloglomerular feedback has recently been reported to be relatively normal in the FHH, the most likely explanation for the impairment in RBF autoregulation in FHH rats in the present study is an altered myogenic response (31). In this regard, we have recently obtained direct evidence that the myogenic response of isolated perfused preglomerular arterioles to elevations in transmural pressure is absent in vessels obtained from the kidneys of FHH rats (29).

We also observed that urinary protein excretion was directly dependent on the changes in RPP in FHH rats. The mechanism involved in this unusual pressure natriuretic response may be dependent on the GFR and the impaired autoregulation of RBF and GFR in response to elevations in RPP. Thus the high baseline filtered load of protein and the increment seen when RPP is elevated likely increased the delivered load of protein to a level that exceeds the transport maximum for reabsorption for protein in the proximal tubule. The present observation that protein excretion is directly dependent on the level of RPP in FHH is consistent with previous reports that pharmacological agents that lower blood pressure reduce the degree of proteinuria and delay the onset of glomerular disease in FHH rats (30). Similarly, pharmacological agents that raise systemic blood pressure in the fawn-hooded rat worsen the severity of glomerular damage and proteinuria (27, 28).

In the present study, we also compared the pressure natriuretic responses in the three strains of rats. Previous studies have indicated that the pressure natriuretic relationship is blunted or reset to a higher level of RPP in every genetic model of hypertension examined to date (5, 21). However, in the present study the relationship between urine flow, sodium excretion, and RPP was not altered in 12-wk-old FHH rats relative to values seen in FHL and ACI rats primarily because GFR is elevated in these rats. The slope of the relationship between the fractional excretion of sodium and RPP was significantly reduced in FHH relative to ACI rats; however, it was not different from the levels seen in FHL rats that do not develop hypertension. From this data we have to conclude that the pressure natriuresis relationship is not blunted in 12-wk-old FHH rats. We also measured arterial pressure and the pressure natriuretic response in an additional group of 36-wk-old FHH rats with severe proteinuria and glomerular damage. As would be expected, RBF and GFR were markedly reduced and the pressure natriuresis response was blunted in these rats.

The lack of resetting of the pressure natriuresis relationship in young FHH rats initially was surprising, but it is consistent with the chronic measurements of arterial pressure obtained in the present study. Although we found that MAP was significantly greater in FHH than FHL rats, the level of MAP in FHH rats (121 mmHg) can be considered being in the normal range of pressures that we have previously reported in normotensive strains of rats (14, 21, 26). Moreover, we found that MAPs in old FHH rats with established glomerular disease measured on a normal-salt diet were also in this range. However, as would be expected from the low GFR and blunted pressure natriuresis response, these rats were salt sensitive and MAP rose from 125 ± 4 to 142 ± 4 mmHg during a 7-day period when the rats were fed a high-salt diet (8% NaCl).

The present study provides the first long-term (24 h) measurements of arterial pressure in conscious FHH rats recorded in their home cage under unstressed conditions. All previous measurements of pressure with this strain were done using the tail cuff in restrained rats. Actually, the measurements of systolic pressure in our study are very similar to those previously reported, although diastolic pressure is rather low in this strain. The FHH rat may also be more responsive to stress and may be able to transmit a greater percentage of the systolic pressure to the tail. This would be consistent with a strain of rat that exhibits impaired myogenic tone not only in the kidney but throughout the systemic circulation.

Previous studies have documented that urinary protein excretion rates for these strains at 3 mo of age average 100, 30, and 15 mg/24 h in FHH, FHL, and ACI rats, respectively (24, 25, 27, 28). Also as confirmed in the present study, FHH rats do not exhibit any histological evidence of glomerulosclerosis at 12 wk of age. These findings in combination with the present measurement of arterial pressure indicate that the development of proteinuria in FHH rats precedes the development of outspoken hypertension and histological evidence of glomerular injury. These data also fit with previous observations that the severity of hypertension in FHH rats remains relatively modest until the animals are quite old or the development of a reduced functional renal mass-like form of hypertension due to severe glomerulosclerosis or when the progression of glomerular injury is accelerated by uninephrectomy or blood pressure is pharmacologically elevated using \( N^\circ -\text{nitro-L-arginine methyl ester} \) (24, 27).

Glomerular hyperfiltration and increased \( P_{GC} \) have been implicated as factors determining the susceptibility to develop glomerulosclerosis in hypertension. An impairment in the efficiency of autoregulation obviously could contribute to a greater transmission in pressure to the glomerulus and therefore may contribute the differences in the incidence of glomerular disease seen in different models of hypertension. For example, autoregulation of RBF and GFR is not impaired in spontaneously hypertensive rats but is highly
efficent and is shifted to higher pressures. These animals do not exhibit elevated $P_{GC}$ or develop glomerulosclerosis until very late in the disease process. In contrast, autoregulation of RBF and GFR is impaired in DOCA-salt and reduced renal mass models of hypertension (2, 13). $P_{GC}$ is elevated in both models, and they rapidly develop severe proteinuria and glomerulosclerosis. Autoregulation of RBF and GFR is also impaired and $P_{GC}$ is elevated in the streptocin-induced insulin-dependent model of diabetes, which develops a severe glomerulosclerosis. The only exception is the Dahl S model of hypertension. These animals also rapidly develop glomerulosclerosis, but $P_{GC}$ is still relatively normal and they exhibit no impairment of RBF autoregulation (21).

Perspectives

In summary, the present study indicates that autoregulation of RBF is impaired in FHH rats, which leads to hyperfiltration, proteinuria, and the subsequent development of glomerulosclerosis. The mechanisms involved remain to be determined, but it may be due to an impairment in the myogenic response in preglomerular renal arterioles. Further experiments need to be performed to try and link these functional abnormalities in renal hemodynamics observed in the FHH rat with the renal failure genes previously identified. A better understanding of the physiology and genetics in this unique genetic animal model of end-stage renal failure may provide insight into the pathogenesis and treatment of end-stage renal failure in humans.

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