Impaired myogenic autoregulation in kidneys of Brown Norway rats

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Wang, Xuemei, David O. Ajikobi, Fred C. Salevsky, and William A. Cupples. Impaired myogenic autoregulation in kidneys of Brown Norway rats. Am J Physiol Renal Physiol 278: F962–F969, 2000.—The Brown Norway (BN) rat is normotensive and has an extended lifespan but is extremely sensitive to hypertension-induced renal injury. Relative impairment of autoregulation has been implicated in the progression of renal failure whereas absence of myogenic autoregulation is associated with early renal failure. Therefore, we tested the hypothesis that there is conditional failure of renal autoregulation in BN rats. In isoflurane-anesthetized BN rats, the pressure-flow transfer function was normal when pressure fluctuated spontaneously. External forcing increased pressure fluctuation and exposed weakness of the myogenic component of autoregulation; the component mediated by tubuloglomerular feedback was less affected. In the absence of vasopressin to raise renal perfusion pressure, myogenic autoregulation was further impaired during forcing in BN rats but not in Wistar rats. Compensation by the myogenic system was rapidly restored on cessation of forcing, suggesting a functional limitation rather than a structural failure. Graded forcing in Wistar rats and in spontaneously hypertensive rats revealed that compensation due to the myogenic system was strong and independent of forcing amplitude. In contrast, graded forcing in BN rats showed that compensation was reduced when fluctuation of blood pressure was increased but that the reduction was independent of forcing amplitude. The results demonstrate conditional failure of myogenic autoregulation in BN rats. These acute studies provide a possible explanation for the observed sensitivity to hypertension-induced renal injury in BN rats.

renal blood flow; transfer function; dynamics; spontaneously hypertensive rat; Wistar; arginine vasopressin

IT IS BELIEVED THAT GENETIC factors play an important role in susceptibility to hypertension-induced renal damage (9, 29). Thus the spontaneously hypertensive rat (SHR) normally develops renal injury slowly, despite high arterial pressure (P_a), whereas the fawn-hooded hypertensive rat is modestly hypertensive and dies of renal failure at ~1 yr of age (29, 31). Renal autoregulation is effective in SHR (7, 32) and very poor in fawn hooded hypertensive rats (27, 30). In several models of renal failure, relative failure of autoregulation has been implicated as contributing to hypertension-induced injury (4, 20). In this respect, the Brown Norway (BN) rat is potentially very interesting.

The BN rat is normotensive and has an extended life expectancy of ~130 wk (22). In comparison, life expectancy is ~55 wk in Fawn-hooded rats (31), ~75 wk in SHR (24), and ~104 wk in Wistar and Sprague-Dawley rats. When normotensive, the BN rat remains free of renal disease. It is, however, very sensitive to hypertension-induced renal injury. Churchill et al. (9) performed cross-transplant studies between BN rats and histocompatible SHR. Each recipient retained one native kidney and received a second kidney either from a rat of the same strain or from the other strain. BN and SHR kidneys transplanted into BN rats functioned normally; neither developed proteinuria or glomerular lesions. Similarly, SHR kidneys transplanted into SHR functioned normally and did not develop proteinuria. However, BN kidneys transplanted into SHR rapidly developed progressive proteinuria and renal injury. The authors concluded that BN rats are 16-fold more sensitive than SHR to hypertension-induced renal damage (9).

There is theoretical (3, 12) and experimental (20, 27, 30) evidence that the faster, myogenic component of renal autoregulation is necessary to efficient stabilization of renal blood flow (RBF) and glomerular capillary pressure. Because a congenital absence of myogenic autoregulation leads to early and severe renal disease (27, 20, 30), we tested the hypothesis that there is a conditional failure of myogenic autoregulation in BN rats.

METHODS

All experiments were performed in 10- to 12-wk-old male rats. BN rats were obtained from Harlan Sprague Dawley (RijHsd colony) for the first experiment and from Charles River (Canada) for the remaining experiments. All other rats were obtained from Charles River. The study was approved by the Sir Mortimer B. Davis Institute-Jewish General Hospital Animal Care Committee and the McGill University Animal Care Officer and conducted under the guidelines promulgated by the Canadian Council on Animal Care. Rats had free access to water and food at all times.

Procedures

Twenty minutes before anesthesia, each rat received the narcotic analgesic buprenorphine (Temgesic, 0.01 mg/kg ip, Reckitt and Colman Pharmaceuticals, Wayne, NJ). Anesthe-
was induced by 5% isoflurane in inspired gas (30% O2-70% air). After induction the anesthetic concentration was reduced to ~2%. The animal was transferred to a servo-controlled, heated table to maintain body temperature at 37°C, intubated, and ventilated by a pressure-controlled small animal respirator (Kent, RSP 1002) operating in respiratory-assist mode. During the 1-h postsurgical equilibration period, inspired anesthetic concentration was titrated to the minimum concentration that precluded a Pa response when the tail was pinched.

Cannulas were placed in a femoral artery (PE-90 with narrowed tip) and vein (PE-50); the venous line contained a Silastic insert to allow drug infusion. A constant infusion delivered 1% of body wt/h; this infusion continued throughout the experiment and contained 2% charcoal-washed bovine serum albumin in normal saline. The left kidney was approached by a left subcostal flank incision. It was immobilized in a plastic cup and covered with plastic wrap. The flow probe was placed after the renal artery was stripped from hilus to aorta. Femoral arterial pressure was measured by a pressure transducer (HP 1290C) driven by a Stentech GPA-1 amplifier. RBF was measured by a Transonic Systems T106 transit time ultrasound flowmeter (RI probe).

A motorized clamp was placed on the aorta between the right and left renal arteries and was used to increase the amplitude of pressure fluctuations. The motor was driven by a program implemented in HP-VEE7. Briefly, the program operates as a negative-feedback controller to maintain downstream pressure ~15% below the spontaneous level of Pa. It iterates at ~1.4 Hz, and at each iteration the target pressure is randomly changed within a range defined by the operator. Except where specifically mentioned, this range was ±10% of the spontaneous Pa.

Experiments

Protocol 1. The first experiment was designed to show whether autoregulation is impaired in BN rats. Eight BN rats obtained from Harlan were studied under conditions of spontaneous Pa fluctuation and again during forcing. The forcing procedure requires renal perfusion pressure to be reduced. Therefore, in seven of the rats a third record was acquired during intravenous infusion of arginine vasopressin (AVP; 8 ng·kg⁻¹·min⁻¹) to enable forcing with renal perfusion pressure at or near the original spontaneous Pa. As a control, the same protocol was also followed in eight Wistar rats.

Protocol 2. The first experiment showed that myogenic autoregulation was impaired during forcing in BN rats. The second experiment was designed to show whether this weakness was reversible. In six BN rats obtained from Charles River, the initial control period (spontaneous Pa) was followed by a 20-min forcing period, then by 1 h of continuous recording with spontaneous Pa fluctuation. Transfer functions were calculated for the first and last 20 min of this hour.

Protocol 3. The second experiment showed a reversible impairment of myogenic autoregulation. Graded forcing was used to determine whether the impairment is due to reduced capacity (early saturation) or to reduced responsiveness of the myogenic system. It was reasoned that if the system saturated early then fractional compensation would decrease progressively as Pa fluctuation was increased. In contrast, if there was reduced responsiveness then one would expect to see low fractional compensation that was independent of forcing amplitude. Graded forcing was applied in eight BN rats obtained from Charles River. After the initial spontaneous period, the target range was progressively increased from ±5 (n = 7) to ±10 (n = 6) and then to ±15% (n = 6). Seven Wistar rats and seven SHR were also tested at the ±10 and ±15% forcing levels. SHR were included because this strain is known to have highly effective autoregulation (7, 32) and because SHR served as the control for the cross-transplant studies of Churchill et al. (9).

Data Acquisition and Analysis

Pressure and flow were digitized on-line. The input (Pa) and output (RBF) signals were filtered at 20 Hz and sampled at 48 Hz by using 12-bit analog-to-digital conversion. Data segments of 1,024 s were band-pass filtered (0.004 and 1 Hz) by using a fast Fourier transform (FFT)-inverse FFT filter (23) with a rectangular window and subsampled to 2 Hz.

Power spectra, transfer functions, and coherences based on the FFT were computed with the use of standard algorithms as shown previously (1, 10, 33), using 512-point segments shaped by the Hann window. Power spectra employed a 50% overlap whereas transfer functions and coherences employed a 69% overlap. Coherence is an index of the degree to which the input and output signals are linearly related; coherence = 1 means that all variation in the output variable can be explained as a linear function of variation of the input, whereas coherence = 0 suggests that the signals are unrelated. Gain in decibels was calculated as 20 · \log (admittance/magnitude/conductance). Thus gain >0 means that Pa fluctuations are amplified into blood flow as expected from passive, compliant vessels; gain = 0 means that the vasculature behaves as a stiff tube; gain <0 means that flow is actively being stabilized, for instance, by autoregulation.

The myogenic system in rat kidneys typically operates at ~0.2 Hz and stabilizes RBF below ~0.1 Hz, whereas tubuloglomerular feedback (TGF) operates at 0.03–0.05 Hz and contributes to stabilization of RBF at lower frequencies (1, 17, 33). To assess the contribution of the myogenic system to stabilization of RBF, we determined fractional compensation in the interval between the operating frequencies of the two systems. The interval from 0.06 to 0.09 Hz was used to minimize corruption by TGF (<0.06 Hz) and by myogenic transients (<0.09 Hz). Fractional compensation is calculated from gain: fractional compensation = 1 – [10\log(gain/20)], which linearizes the logarithmic scale of gain. Thus fractional compensation = 1 implies complete autoregulation, and fractional compensation = 0 implies total absence of autoregulation.

As an index of the amplitude of Pa fluctuation, Pa spectral power was integrated over the interval from 0.06 to 0.09 Hz (I06-09). Because I06-09 was not normally distributed (variance proportional to mean), the square root transformation was applied before statistical testing. Differences within and among experiments were assessed by one-way ANOVA and completed by the least significant difference test. Results are presented as means ± SE. P < 0.05 was considered to be significant.

RESULTS

Averages for all experiments of Pa, RBF, and I06-09 are reported in Table 1. As expected SHR had higher Pa than Wistar and BN rats. Although Pa in the BN rats tended to be higher than that of the Wistar rats, the values are within the range previously reported from this laboratory for Wistar rats (1, 33). Also, several BN rats with low spontaneous Pa (<90 mmHg) were excluded because forcing could not be achieved with reasonable renal perfusion pressure. The observed
were dominated by linear behavior in the passive coherence in both strains indicates that RBF dynamics were studied under three conditions, control (spontaneous Pa fluctuation), Forced (Pa), Forced + AVP (7), BN and Wistar rats. High renal vasoconstriction in the two strains. With spontaneous Pa fluctuation, AVP, which was effective under conditions of spontaneous Pa fluctuation but was reduced during forcing, P < 0.01, and further reduced during forcing+AVP, P < 0.01.

Experiment 2 was designed to confirm conditional impairment of autoregulation in BN rats from another source (Charles River) and to show whether the impairment of myogenic autoregulation in BN rats is reversible. RBF dynamics were assessed beginning immediately after forcing was stopped (R1) and beginning 40 min after forcing was stopped (R2). As shown in Table 1, Pa, RBF, and I_{06-9} were comparable in the two recovery periods and were not different from those seen in the initial control period. Dynamic results from this experiment are presented in Fig. 3; for clarity, only the forcing and immediate recovery (R1) periods are shown. Significant increases in Pa fluctuation were achieved only below 0.3 Hz (Fig. 3, top). Coherence (Fig. 3, middle) was high at all frequencies examined when Pa was forced; under conditions of spontaneous Pa fluctuation, coherence tended to decline below 0.1 Hz. In the band from 0.06 to 0.09 Hz, it was 0.61 ± 0.05, 0.96 ± 0.01, 0.66 ± 0.11, and 0.55 ± 0.10 in the control, forced, early (R1), and late (R2) recovery periods, respectively. Admittance gains are shown in Fig. 3 (bottom). There was rapid restoration of normal RBF gain when forcing was stopped. Figure 4 shows that fractional compensation was reduced during forcing (P = 0.05 vs. control), was rapidly restored (P < 0.01 vs. forcing), and was stable for 60 min after forcing (P < 0.05 vs. forcing).

Experiment 3 tested the response of myogenic autoregulation in BN and Wistar rats and in SHR to graded forcing. As shown in Fig. 5 (top) and Table 1, graded increments of Pa spectral power and I_{06-9} were achieved in all three strains. As expected, coherence was high at all frequencies > 0.03 Hz when Pa was forced, as shown in Fig. 5 (middle). Under conditions of spontaneous Pa fluctuation, coherence declined modestly below 0.2 Hz, particularly in SHR. Figure 5 (bottom) shows that, in BN rats, gain reduction by the myogenic system was reduced during forcing. In contrast, gain reduction by the myogenic system in Wistar rats and SHR was not affected by forcing amplitude. Figure 6 summarizes

### Table 1. Hemodynamic status of rats

<table>
<thead>
<tr>
<th>Experiment No/Strain</th>
<th>Condition</th>
<th>Pa (mmHg)</th>
<th>RBF (ml/min)</th>
<th>I_{06-9}</th>
</tr>
</thead>
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<tr>
<td>1 BN</td>
<td>Spontaneous (8)</td>
<td>125 ± 5</td>
<td>3.5 ± 0.4</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>BN</td>
<td>Forced (8)</td>
<td>105 ± 5</td>
<td>3.3 ± 0.3</td>
<td>12 ± 1†</td>
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<tr>
<td>BN</td>
<td>Forced + AVP</td>
<td>124 ± 4</td>
<td>2.5 ± 0.1</td>
<td>52 ± 22‡</td>
</tr>
<tr>
<td>BN</td>
<td>Spontaneous</td>
<td>110 ± 2</td>
<td>4.4 ± 0.3</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>BN</td>
<td>Forced</td>
<td>101 ± 1</td>
<td>4.7 ± 0.4</td>
<td>29 ± 2*</td>
</tr>
<tr>
<td>BN</td>
<td>Forced + AVP</td>
<td>117 ± 2</td>
<td>3.8 ± 0.4</td>
<td>36 ± 4*</td>
</tr>
<tr>
<td>BN</td>
<td>Spontaneous</td>
<td>113 ± 5</td>
<td>4.0 ± 0.2</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>BN</td>
<td>Forced</td>
<td>92 ± 3</td>
<td>3.5 ± 0.2</td>
<td>58 ± 20*</td>
</tr>
<tr>
<td>BN</td>
<td>Recovery R1</td>
<td>108 ± 4</td>
<td>3.6 ± 0.1</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>BN</td>
<td>Recovery R2</td>
<td>107 ± 6</td>
<td>3.6 ± 0.1</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>BN</td>
<td>Spontaneous</td>
<td>113 ± 6</td>
<td>4.3 ± 0.4</td>
<td>1.8 ± 0.6</td>
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<tr>
<td>BN</td>
<td>Forced-low (7)</td>
<td>107 ± 6</td>
<td>4.7 ± 0.7</td>
<td>9.9 ± 1.2*</td>
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<tr>
<td>BN</td>
<td>Forced-medium (6)</td>
<td>103 ± 8</td>
<td>3.8 ± 0.2</td>
<td>21.4‡</td>
</tr>
<tr>
<td>BN</td>
<td>Forced-high (6)</td>
<td>106 ± 6</td>
<td>5.0 ± 0.7</td>
<td>42 ± 10*</td>
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<tr>
<td>BN</td>
<td>Spontaneous</td>
<td>105 ± 4</td>
<td>4.5 ± 0.4</td>
<td>11.0 ± 0.2</td>
</tr>
<tr>
<td>BN</td>
<td>Forced-medium</td>
<td>91 ± 3</td>
<td>4.0 ± 0.3</td>
<td>14 ± 1.9*</td>
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<tr>
<td>BN</td>
<td>Forced-high</td>
<td>97 ± 2</td>
<td>3.9 ± 0.2</td>
<td>34 ± 4‡</td>
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<tr>
<td>BN</td>
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<td>153 ± 9</td>
<td>6.6 ± 0.8</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>BN</td>
<td>Forced-medium</td>
<td>125 ± 8</td>
<td>6.8 ± 0.6</td>
<td>37 ± 8*</td>
</tr>
<tr>
<td>BN</td>
<td>Forced-high</td>
<td>122 ± 7</td>
<td>6.7 ± 0.6</td>
<td>71 ± 12‡</td>
</tr>
</tbody>
</table>

Values are means ± SE, with no. of rats in parentheses. Pa, arterial pressure, mmHg; RBF, renal blood flow (ml/min); I_{06-9}, integrated Pa spectral power (mmHg²); recovery R1 and R2, records acquired just after forcing stopped and 40 min later respectively; BN, Brown Norway rats; SHR, spontaneously hypertensive rats. *P < 0.01 vs. previous period; †P < 0.05 vs. control; ‡P < 0.01 vs. previous period; §P < 0.01 vs. all other periods.
experiment 3; it shows fractional compensation plotted against $I_{06-09}$. Fractional compensation was similar in the three strains when $P_a$ fluctuated spontaneously and was independent of $I_{06-09}$ in Wistar rats and in SHR. In contrast, fractional compensation was reduced from control by forcing in BN rats ($P < 0.05$) but was not different among the different levels of forcing.

DISCUSSION

The BN rat is normotensive and long lived but very sensitive to hypertension-induced renal and cerebral vascular injury (5, 9, 14). This study was performed to test the hypothesis that there is conditional failure of renal autoregulation in BN rats. The hypothesis arises from the linkage between efficiency of autoregulation and progression of renal disease in several models (4, 20, 25) and from the observation that constitutive failure of myogenic autoregulation in fawn-hooded hypertensive rats is associated with early appearance of glomerular lesions and a short lifespan (27, 30). The results demonstrate conditional impairment of myogenic autoregulation in BN rats. They show that, under conditions of spontaneous $P_a$ fluctuation, the pressure-dependent regulation of RBF appears normal but external forcing exposes significant limitation of the myogenic system. In comparison similarly treated Wistar rats and SHR exhibited effective myogenic autoregulation that was independent of forcing amplitude.

The Brown Norway rat has been used extensively for immunological studies, but surprisingly little is known about the kidney and its function in this inbred strain. Brown Norway rats were acquired from two sources (Charles River and the Harlan RijHsd colony); both exhibited the conditional failure of renal autoregulation. In general, BN rats showed average $P_a$ that was similar to the present results with Wistar rats. Al-
though Pa was slightly higher in the Harlan rats, this level (125 ± 6 mmHg) is within the range we have reported previously for Wistar and Sprague-Dawley rats anesthetized by isoflurane (1, 10, 33). At any given body weight, both groups of BN rats have significantly smaller kidneys than do Wistar rats. The BN rats from Harlan appeared to have smaller kidneys than those from Charles River. The BN rats from Harlan showed a strong local maximum in gain at ~0.04 Hz. Such a pronounced resonance peak due to TGF is seen in dogs (19) but is not normally observed in rats (e.g., 1, 7, 10, 18, 20, 33). In this respect the BN rats from Charles River more closely resemble other normotensive strains.

Broad-band forcing of the input variable (Pa), with approximately equal spectral power at all relevant frequencies, is a commonly used strategy to aid in system identification (17). We anticipated that using a suprarenal aortic clamp as a feedback controller of renal perfusion pressure with the target pressure being randomly changed at each iteration (0.7-s interval) would provide broad-band fluctuation of Pa. In experiments 1 and 3, Pa spectral power was increased at all frequencies below 1 Hz (Figs. 1 and 5), whereas in experiment 2 Pa power was increased only below 0.3 Hz (Fig. 3). In all cases, the Pa spectra were flat from 0.1 to at least 0.004 Hz (data not shown). The distinct reduction of Pa power above 0.1 Hz is probably due to vascular compliance because the roll-off becomes much smaller when the mesenteric, and particularly the hindquarter, vascular beds are removed from the circulation (Ref. 7, unpublished observations). Two factors led to the decision to tolerate the reduction of Pa power above 0.1 Hz. First, Pa values the spectra achieved are adequate for linear analysis and the relationship between Pa and RBF is well captured by linear methods, as documented by the coherence spectra presented in Figs. 1, 3, and 5. Second, other methods of forcing (discussed in Ref. 17) require significantly more surgical manipulation of the animal. The latter consideration is of some practical importance as BN rats are less robust in their tolerance of surgical insult than are Wistar rats and SHR.

Experiment 1 was designed to demonstrate conditional failure of autoregulation in BN rats. Compared with the classic gain spectrum (e.g., 1, 13, 18) seen during control, the BN rats showed clear and significant impairment of myogenic autoregulation during forcing, whereas autoregulatory efficiency was not affected in equivalently forced Wistar rats. Because the forcing strategy used requires reduction of renal perfusion pressure, infusion of AVP, which does not impair myogenic autoregulation in Wistar rats (Fig. 1 and Ref. 33), was included to permit forcing at the original spontaneous Pa and thus to provide a control for the pressure reduction. Surprisingly, infusion of AVP further impaired myogenic autoregulation in BN rats. Thus, although informative in its own right, experiment 1 did not provide a pressure control. We do know, however, from recent preliminary reports that the gain of steady-state renal autoregulation is reduced in BN rats (16) when renal perfusion pressure is varied above 100 mmHg and that myogenic autoregulation operates, albeit weakly, in the normal range of perfusion pressure above 90 mmHg (2).

AVP caused equivalent renal vasoconstriction in the two strains as conductance was reduced by 30 ± 3% in Wistar rats and by 39 ± 5% in BN rats. We also see normal renal vasoconstriction in BN rats on inhibition of nitric oxide synthase (11), suggesting that agonist-

![Fig. 3. Rapid recovery of myogenic autoregulation in BN rats. Results acquired during forcing (heavy line) and immediately after forcing stopped (R1; Ô) are shown. Top: Pa spectral power, which was increased below 0.3 Hz by forcing. Middle: coherence. Bottom: admittance gain. During forcing, reduction of gain by myogenic system was considerably attenuated.](http://ajprenal.physiology.org/)

![Fig. 4. Effect of forcing and its cessation on fractional compensation in BN rats. Values are means ± SE; n = 6. Fractional compensation was normal in initial CTL period, was significantly reduced during forcing, and was normal during R1 and late recovery period (R2; 40 min after end of forcing). *Significantly different from CTL (P = 0.05), from R1 (P < 0.01), and from R2 (P < 0.05).](http://ajprenal.physiology.org/)
induced vasoconstriction is intact in these rats. This, in turn, suggests that the contractile machinery of the vascular smooth muscle is intact, as is also the case in the fawn-hooded hypertensive rat (28), and that the event leading to impaired autoregulation is specific to the myogenic system.

The mechanism leading to the interaction between AVP and the myogenic system in BN rats is presently unknown. One possibility would be that AVP preferentially constricts large arteries (6), thus reducing pressure at the afferent arteriole to levels below the normal operating range of the myogenic mechanism. Given the similar Pa achieved in the two groups, plus the similar, modest reductions of renal vascular conductance, and the apparently normal range of pressure in which the myogenic mechanism operates (2), this seems unlikely. Another possibility arises from the fact that both AVP-induced renal vasoconstriction (26) and myogenic responses (15) are largely dependent on Ca2+ entry through L-type channels. It is therefore conceivable that limitation of Ca2+ entry may be a site for interaction between myogenic autoregulation and AVP in BN rats. It also tends to suggest a signaling abnormality in the myogenic system of BN rats.

Experiment 2 was designed to test whether normal RBF autoregulation was restored when forcing was stopped. The rationale was that if the forcing was causing vascular injury (i.e., a structural lesion) then normal autoregulation would be restored slowly, if at all, in an acute experiment. If, however, the impair-

**Fig. 5.** Effect of graded forcing on renal blood flow (RBF) dynamics in BN (A; n = 8, 7, 6, and 6) and Wistar (B; n = 7), and in spontaneously hypertensive rats (SHR; C; n = 7) on Pa spectral power (top), coherence (middle), and admittance gain (bottom). After CTL period (spontaneous Pa fluctuation; thick lines), forcing was applied at low (only in BN rats: ○), medium (MED; □), and high (△) amplitudes. Admittance gain in Wistar rats and SHR was unaffected by increased forcing amplitude, whereas gain reduction below 0.2 Hz in BN rats was attenuated when Pa fluctuation was increased.

**Fig. 6.** Effect of graded forcing on myogenic autoregulation. Fractional compensation is plotted as function of integrated Pa spectral power in interval between 0.06 and 0.09 Hz (I₀.₀₆₋₀.₀₉). Values are means ± SE; n = 8, 7, 6, and 6 BN; 7 Wistar; and 7 SHR. In Wistar rats and SHR, fractional compensation was independent of I₀.₀₆₋₀.₀₉. In BN (B-N) rats, fractional compensation was similar to that in Wistar rats (WIS) and to SHR under spontaneous conditions and declined when Pa was forced (P < 0.05). However, fractional compensation showed no further dependency on Pa fluctuation as forcing amplitude was increased.
ment of autoregulation was functional, then rapid restoration of normal RBF dynamics would be expected. The results show that normal autoregulation was restored rapidly when forcing was stopped and that there were no further demonstrable changes in RBF dynamics over the following hour. We infer, therefore, that there is some functional limitation rather than a structural lesion.

Experiment 3 was designed to begin the exploration of how the myogenic system is limited in BN rats. It was reasoned that normal sensitivity to $P_a$ fluctuation combined with limited capacity to alter renal conductance would result in decreasing fractional compensation as forcing amplitude was increased. However, if sensitivity were reduced then one would expect fractional compensation to be low and independent of $P_a$ fluctuation. As expected (8), the myogenic system in Wistar rats and SHR isolated the kidney from a high and relatively constant fraction of $P_a$ fluctuation over a wide range of input amplitude, expressed as I_{25.00}. The contrast between BN rats on the one hand and Wistar rats and SHR on the other is quite striking. In BN rats, fractional compensation decreased when forcing was applied but did not decline further when progressively stronger forcing was applied. The result is clear and not explained simply by reduced capacity to adjust resistance nor by reduced sensitivity to $P_a$ fluctuation. Instead, it suggests a third possibility: when $P_a$ fluctuation is small, the myogenic system operates in a manner similar to that seen in other rats; when $P_a$ fluctuation is increased, in this case by external forcing, the system appears to switch to another mode of operation.

The results demonstrate a conditional impairment of renal autoregulation in BN rats that resides in the myogenic system, is functional rather than structural, and is associated with an abnormal interaction with the vasoconstrictor AVP. The relative failure of myogenic autoregulation may involve a change in the internal behavior of the system when $P_a$ fluctuation increases. If the results obtained in these anesthetized rats reflect operation of autoregulation in conscious BN rats, then the limitation in autoregulation could provide an explanation for the exquisite sensitivity to hypertension-induced renal injury shown by these animals. In this light, it is perhaps noteworthy that the $P_a$ fluctuation achieved during forcing in the present study is quite comparable to that seen in unforced conscious Wistar rats and SHR (21).

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*Incommensurate frequencies of major vascular regulatory mechanisms.*