Attenuated buffering of renal perfusion pressure variation in juxtamedullary cortex in SHR

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Roald, Anca B., Jarle Ofstad, and Bjarne M. Iversen. Attenuated buffering of renal perfusion pressure variation in juxtamedullary cortex in SHR. Am J Physiol Renal Physiol 282: F506–F511, 2002; 10.1152/ajprenal.00199.2001.—Renal tissue damage is substantially more pronounced in the juxtamedullary than in the superficial cortex in hypertensive rats, and the pathogenesis of the morphological changes are only partly understood. Glomerular capillary pressure (PGC) is increased, and steady-state autoregulation is normal in the deep renal cortex. We tested the hypothesis that the transient period from one pressure level to another may induce greater variation in local perfusion before stable autoregulation is established. An acute increase in local perfusion was compared in the superficial and juxtamedullary cortex of spontaneously hypertensive (SHR) and Wistar-Kyoto rats (WKY) after an abrupt increase in perfusion pressure. Total renal blood flow (RBF) was measured by a Transonic flow probe and local renal perfusion by laser Doppler flowmetry. Renal perfusion pressure was lowered to 50% of initial values and released abruptly. The maximal RBF increased from 6.3 ± 0.4 to a maximal value of 7.6 ± 0.3 ml/min (P < 0.001) in SHR and from 7.3 ± 0.3 to 8.2 ± 0.6 ml/min (P < 0.001) in WKY. These changes were not significantly different from each other. The change in superficial cortical perfusion was also not different between SHR and WKY. Pressure release increased juxtamelular perfusion in SHR from 146 ± 8 to a maximal value of 228 ± 17 units (P < 0.001) and in WKY from 160 ± 13 to 179 ± 11 units (P < 0.001). The results were significantly different from each other (P < 0.001). The time for maximal flow response was shorter in the deep cortex of SHR, and the time for normalization was longer than in WKY. These data indicate that the buffering of perfusion pressure variation is significantly attenuated in the juxtamedullary cortex, and significantly more so in SHR than in WKY, assuming a covariation of RBF and PGC, and this finding may explain the extensive morphological damage in the juxtamedullary cortex of SHR.

renal blood flow; glomerular filtration rate; renal cortex; spontaneously hypertensive rat

The pathogenesis of hypertensive renal damage is only partly understood; increased glomerular capillary pressure (PGC) and blood flow are considered to be main pathogenic factors (12). This is supported by our recent finding of increased PGC and glomerulosclerosis index in the juxtaglomerulary cortex of 10-wk-old spontaneously hypertensive rats (SHR); the juxtaglomerulary PGC in SHR also increased with age, whereas the superficial PGC remained unaltered (8). This corresponds to the observation that glomerulosclerosis in superficial glomeruli is a late finding in SHR. A moderately increased PGC in superficial glomeruli has been reported in another study (1).

Theoretically, hypertensive damage of the juxtamedullary cortex may be caused by attenuated autoregulation of PGC in this cortical layer, exposing the glomerular capillaries to a PGC increase pari passu with an increase in the renal perfusion pressure (RPP). However, in previous studies we have demonstrated that autoregulation of neither glomerular filtration rate (GFR; aprotinin method) nor local renal blood flow (RBF; laser Doppler flowmetry) is reduced in the juxtaglomerulary cortex of young and old SHR (8, 20). As autoregulation of PGC is similar to GFR and RBF, there is therefore no reason to assume that established PGC autoregulation was attenuated in these animals.

The observed similarity of established autoregulation in different cortical layers, however, does not exclude that PGC, RBF, and GFR in these layers were different in that portion of the transition period from the first established state of autoregulation to the next. Immediately after an acute increase in perfusion pressure, there is an abrupt and parallel increase in RBF and, probably, also in PGC before stable autoregulation is obtained; this phase represents the time it takes for the smooth muscle cells in the resistance vessels to adjust to the new pressure.

Autoregulation of RBF, GFR, and PGC involves both the tubuloglomerular feedback (TGF) system and a myogenic mechanism (11). The myogenic component of autoregulation is fast, probably involves both the interlobular artery and afferent arterioles, and is based on an autonomous reaction of the arterial smooth muscle cells on changes in wall stretch. The TGF compo-

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measure RPP. The left femoral vein was cannulated for by insertion of a short polyethylene (PE)-260 tube, a PE-50 tal sodium anesthesia (50 in rats, which had been fasted overnight, under pentobarbi-

The purpose of the present study was to examine the immediate response to a pressure increase before au-
toregulation of flow is stabilized in SHR using Wistar-Kyoto rats (WKY) as controls. The pressure increase was obtained by lowering the blood pressure to ~50% of control pressure and then abruptly releasing it. The total blood flow response as well as local perfusion from superficial and juxtamedullary cortex to this pressure increase were recorded using a flow probe and the laser Doppler technique.

MATERIALS AND METHODS

Animals. A total of eight male SHR and seven WKY, aged 20–25 wk, were used in study. All rats had free access to water and were fed ordinary rat chow (B&K Universal) containing 0.30% sodium, 0.70% potassium, 0.88% calcium, and 18% crude protein. All experiments were performed in accordance with and under the approval of the Norwegian State Board for Biological Experiments with Living Animals.

Hemodynamic study. The measurements were carried out in rats, which had been fasted overnight, under pentobarbi-
tal sodium anesthesia (50–60 mg/kg). After a tracheostomy by insertion of a short polyethylene (PE)-260 tube, a PE-50 catheter was placed into the aorta below the renal arteries to measure RPP. The left femoral vein was cannulated for infusion of 5% bovine serum albumin in 0.9% sodium chloride solution at a rate of 1.0 ml·100 g body wt⁻¹·h⁻¹ to keep the hematocrit constant. The left kidney was exposed through a midline abdominal incision and dissected free, and care was taken not to denervate the kidney. It was placed in a Lucite plastic cup with the dorsal aspect facing upward and immo-
bilized by cotton moistened in saline. A flow probe connected to a transit-time flowmeter (Transonic), and a Gould recorder was used to measure total RBF. The probe was calibrated in vitro. A sling of thread was placed around the aorta above the renal arteries for reduction of RPP.

Laser Doppler flowmetry. Local renal cortical perfusion was measured by the laser Doppler technique (Periflux 4001; Perimed, Stockholm, Sweden). The superficial probe was placed on the surface of the kidney; the needle probe was introduced 2–3 mm from the surface of the kidney for mea-
surements of juxtamedullary cortical perfusion. Cortical perfu-
sion was expressed in arbitrary units or in percent change from baseline values. After surgery, the animals were allowed to rest for 30 min.

Table 1. Body weight, kidney weight, mean arterial pressure, total renal blood flow, and superficial and juxtamedullary cortical perfusion in WKY and SHR

<table>
<thead>
<tr>
<th></th>
<th>Body Wt, g</th>
<th>Kidney Wt, g</th>
<th>MAP, mmHg</th>
<th>Total RBF, ml/min</th>
<th>Superficial Cortical Flow, PU</th>
<th>Juxtamedullary Flow, PU</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>380 ± 5</td>
<td>1.25 ± 0.3</td>
<td>112 ± 14</td>
<td>7.3 ± 0.3</td>
<td>543 ± 16</td>
<td>160 ± 13</td>
</tr>
<tr>
<td>SHR</td>
<td>362 ± 6</td>
<td>1.29 ± 0.2</td>
<td>150 ± 6*</td>
<td>6.3 ± 0.4</td>
<td>482 ± 39</td>
<td>146 ± 8</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 Wistar-Kyoto (WKY) rats and 8 spontaneously hypertensive rats (SHR). MAP, mean arterial pressure; RBF, renal blood flow; PU, perfusion units. *P < 0.001, SHR vs. WKY.

RESULTS

The control data are shown in Table 1. MAP was significantly higher in SHR than in WKY (P < 0.001). The baseline renal hemodynamic values were all slightly lower in SHR, but no significant difference was seen in the control period after 30 min of rest after surgery (Table 1).

The maximal RBF increase when blood pressure was reduced for 6–8 s and then abruptly released was not different in SHR and WKY; although this increase tended to be higher in SHR, the difference did not reach significance (P > 0.1) (Fig. 1). The maximal increase in total RBF was significant in both strains (Fig. 1). In SHR, RBF increased from 6.3 ± 0.4 to 7.6 ± 0.3 ml/min (P < 0.001). The comparable increase in
WKY was from 7.3 ± 0.3 to 8.2 ± 0.6 ml/min (P < 0.001).

The superficial perfusion was 482 ± 39 units in SHR and, after the pressure release, it increased to a maximum of 548 ± 44 units (P < 0.001). The corresponding values in WKY were 543 ± 16 and 593 ± 18 units (P < 0.01). The magnitude of the responses in SHR and WKY was not significantly different in the superficial cortex (P > 0.2) (Fig. 2).

In SHR the results obtained from the juxtamedullary cortex were significantly different from those obtained in the superficial cortex. The baseline values were not different (P > 0.3); acute pressure release increased juxtamedullary perfusion in SHR from 146 ± 8 to 228 ± 17 units (P < 0.001) and in WKY from 160 ± 13 to 179 ± 11 units (P < 0.001) (Fig. 3). The difference in local perfusion response between SHR and WKY was highly significant (P < 0.001).

An example of a representative recording from the superficial and juxtamedullary cortex is shown in Fig. 4. After a stable baseline value was obtained, blood pressure was reduced and abruptly released. Perfusion increased over baseline in both WKY and SHR, but the response was significantly higher in SHR compared with WKY. The maximal increase compared with control was recorded, as was the time from pressure release to the maximal response and normalization of local perfusion in superficial and juxtamedullary cortex in both animal strains.

When the response to the pressure release was calculated as percent change from control values (100%), the total RBF increase to 121 ± 4 in SHR and to 111 ± 5% in WKY. The difference between these responses was not significantly different (P > 0.5). Superficial cortical perfusion in SHR increased to 114 ± 2 and 110 ± 3% in WKY. The difference between these responses was not significantly different (P > 0.3). In the juxtamedullary cortex, perfusion increased to 157 ± 9 in SHR and to 113 ± 3% in WKY. This difference in response was highly significant (P < 0.0001) (Fig. 5).

The time from perfusion pressure release and the maximal response in superficial cortex was 18 ± 4 in SHR and 19 ± 5 s (P > 0.20) in WKY. In the juxtamedullary cortex, the time for maximal response was 14 ± 3 in SHR and 20 ± 4 s in WKY (P < 0.05). In the superficial cortex of SHR, the time to complete normalization of perfusion pressure was 30 ± 5 s, significantly shorter than in the juxtamedullary cortex, where normal perfusion was obtained after 45 ± 3 s (P < 0.01). These values were not different from those obtained in WKY (25 ± 4 vs. 38 ± 6 s).

DISCUSSION

The main finding in the present study is the attenuated buffering of the perfusion response in the juxtamedullary cortex of SHR during an abrupt increase...
in RPP. An acute change in systemic pressure has also been reported to induce corresponding transient changes in $P_{GC}$ (3). The blood perfusion response is therefore probably also accompanied by a corresponding attenuated buffering of $P_{GC}$ autoregulation. These findings indicate that different autoregulatory patterns in the superficial and deep cortex represent a pathogenic mechanism of the different glomerular damage observed in the deep cortex of SHR. Attenuated buffering of $P_{GC}$ may have an additive effect to the permanently increased $P_{GC}$ in the juxtamedullary cortex of SHR (8), but it may also cause damage in glomeruli without a permanently increased $P_{GC}$. The changes in systemic blood pressure necessary to induce these different patterns of response seem to be present in both awake SHR and WKY observed by a continuous recording of blood pressure (2, 10).

The methodological difficulties in the present study should be taken into account when the data are interpreted. To compare the groups, the perfusion pressure had to be lowered to a pressure level where autoregulation in SHR and WKY was similar, i.e., at the lower pressure limit of autoregulation. At this pressure, direct puncture of deep and superficial glomeruli will, because of the organ-volume changes accompanying substantial variations of the perfusion pressure, induce substantial technical problems. We therefore chose to measure the blood flow response as an indirect expression of $P_{GC}$. Volume changes may also interfere with the laser Doppler measurements, but to a minor extent and only in the low-pressure phase. The local perfusion recordings during the initial pressure reduction were reduced more than could be explained by the blood pressure reduction alone, probably due to volume changes and altered contact between tissue and probes. However, these pressure reductions did not seem to interfere with either the baseline recordings, which were repeated regularly, or the pattern of flow-response, which was also repeatedly achieved. The typical pattern of flow-response was also seen with smaller pressure reductions. The limitations with laser flowmetry should also be taken into account. Although the Doppler signal may not be linear to tissue flow, especially if the flow is reduced to a great extent, the primary goal of the present study was to compare the responses from the superficial and juxtamedullary cortex in WKY and SHR, i.e., to obtain significant differences, not to achieve exact blood flow values. It is therefore reasonable to suggest that the methodology is a sound basis for the interpretation of the present findings.
It is generally accepted that the TGF response is considerably slower than the myogenic response (4, 19). Relative dominance of the TGF response in the deep cortex compared with the superficial nephrons and/or a correspondingly reduced participation of the myogenic component in juxtamedullary nephrons could explain the findings of attenuated autoregulation in the juxtamedullary cortex. In a study of single-nephron GFR (SNGFR) during free flow and after blockade of macula densa flow in intact normotensive kidneys, tubular blockade increased SNGFR from 25.8 to 29 nl/min in the superficial nephrons and tripled the increase, from 27.7 to 84 nl/min, in the deep cortex (5). The effect of distal tubular blockade has been repeated by the same group (6). These observations represent strong evidence that the TGF response is considerably more dominant in juxtamedullary than in superficial nephrons and that TGF probably dominates autoregulation of SNGFR and PGc in the juxtamedullary nephrons in the intact kidney. In the juxtamedullary cortex preparation, a possibly greater myogenic effect on the blood flow response after an abrupt perfusion pressure increase has been reported (19); the myogenic component studied was localized to the afferent arteriole and was also influenced by the TGF response. For obvious reasons, this study did not include corresponding data from the superficial cortex. Casellas and Moore (3) observed in the same preparation that a small but significant area of PGc autoregulation was localized upstream from the afferent arteriole, most probably in the interlobular artery (ILA). There is substantial and more direct evidence that the ILA participates in autoregulation. First, the pressure drop of ~25 mmHg along this vessel is sufficient to permit involvement in autoregulation (14); second, measurements of the afferent arteriolar diameter (microsphere method) during pressure reduction in the intact kidney from Wistar rats indicate that afferent arterioles do not participate in the early phase of autoregulation (13); and third, pressure measurements by direct micropuncture of the ILA during pressure reduction do present convincing evidence that the ILA participates in autoregulation in the intact kidney when the perfusion pressure is reduced (7). As also concluded by Casellas and Moore (3), the potential for participation in autoregulation is probably greater in the superficial than in the juxtamedullary part of the ILA due to the additive effect of contraction along the artery. Taken together, there is conclusive evidence that the TGF response is considerably stronger in the juxtamedullary than in the superficial nephrons and the myogenic part of autoregulation localized to the ILA is probably less in the juxtamedullary than in the superficial cortex. This may explain the attenuated buffering of autoregulation in the juxtamedullary cortex and also the greater glomerular derangement in this part of the kidney.

Casellas and Moore (3) further reported that changing the perfusion pressure within the autoregulatory range with ~20 mmHg induced an acute PGc change of 9 mmHg that was normalized in 60 s. This is supported by the observations from the present study that perfusion in the deep cortex needs 40–45 s to normalize. These observations in addition to those of Ericson et al. (5) support our assumption that the abrupt changes in blood flow in the present study indirectly express concomitant changes in PGc.

When RPP is lowered to or below the lower limit of autoregulation, the TGF signal is maximally reduced, and afferent arterioles are dilated equally and with the same diameter in all cortical layers in both normotensive and hypertensive rats (9). In this situation of low vascular resistance, an acute pressure wave will have a maximal effect on flow and PGc before autoregulation is maintained. As myogenic autoregulation is considerably faster than the TGF response (4), an acute pressure wave will be attenuated more rapidly in the outer than in the inner cortex because the autoregulatory resistance in the deep cortex is more dependent on the slow TGF response than in the superficial layers. Also of importance is that the pulse wave will be reduced in the outer cortex due to the pressure drop along the ILA. This difference may be even greater in hypertensive than in normotensive animals because the pressure drop in the ILA probably increases with increasing perfusion pressure, as has been shown in model studies (15).

In our previous study, a permanent increase in juxtamedullary PGc was found in SHR even at the age of 10 wk, suggesting that the capillary pressure is increased at an early age (8). The instability in the initial phase of autoregulation may thus start the early signs of glomerulosclerosis as a normal phenomenon, which is then accelerated when hypertension is developed (8). In the more advanced stage, nephron loss appears and compensatory growth may start a vicious circle accelerating the development of glomerulosclerosis. In 40wk-old SHR, we have earlier demonstrated that the diameter of the afferent arterioles is increased, possibly due to the growth mechanism (9). This phenomenon may attenuate the buffering effect of the resistance vessels further with rapid development of advanced glomerulosclerosis, as can be seen in 70-wk-old SHR. We have also shown that the glomeruli are larger in the deep compared with the superficial cortex, even in rats with normal pressure (8). This factor may also be of importance as increased growth may be related to development of glomerulosclerosis as well as hypertensive renal damage (16). The effect of increased intraglomerular pressure on growth is also demonstrated by Riser et al. (18). In this study, increased stretching of the mesangial cells increased the synthesis of collagen and other components of the extracellular matrix, indicating that capillary expansion due to increased pressure may provoke glomerulosclerosis (18).

Considerable variations in systolic blood pressure are seen in normotensive as well as hypertensive animals, and the amplitude of these blood pressure variations are substantially increased in hypertensive rats (2). Similar observations have also been made during norepinephrine infusion where the
daily variation in systemic blood pressure increases (10). These observations suggest that, in the hypertensive state, the renal cortical vessels are exposed to greater fluctuations in systemic blood pressure than are normotensive individuals. The oscillation in local RBF and perfusion pressures is probably greater in the deep cortex of hypertensive animals than in that of normotensive ones.

In summary, the different autoregulatory reactions in the juxtamedullary and superficial cortex on an abrupt increase in systemic blood pressure may explain both the different degree of glomerulosclerosis between SHR and WKY and the intracortical difference in glomerulosclerosis observed in both species (8). The longer period to establish stable autoregulation in SHR and WKY and the intracortical difference between SHR and WKY may affect the different degree of glomerulosclerosis in SHR juxtamedullary cortex.

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