Abstract The kidney is probably critically involved in the development of essential hypertension. We have investigated whether a narrowed renal afferent arteriole is involved in the pathogenesis of hypertension in spontaneously hypertensive rats. Systolic blood pressure of 37 F2 generation spontaneously hypertensive rats/Wistar-Kyoto rats was measured at age 7 weeks. The right kidney was removed, and lumen diameter and media cross-sectional area of the afferent arterioles were measured after having been fixed while relaxed and under a transmural pressure of 100 mm Hg. The uninephrectomized rats continued until age 23 weeks, when mean blood pressure was measured. Mean blood pressure at 23 weeks was negatively correlated with lumen diameter at 7 weeks. Quartile analysis based on lumen diameter at 7 weeks showed that compared with rats in the top lumen diameter quartile, rats in the bottom lumen diameter quartile had a reduced media cross-sectional area at 7 weeks (17%), the same systolic blood pressure at 7 weeks, and an increased (16%) mean blood pressure at 23 weeks. We conclude that in spontaneously hypertensive rats a narrowed lumen of distal afferent arterioles at 7 weeks contributes to later development of increased blood pressure. This reduced lumen could be caused by inhibited renal afferent arteriole growth. (Hypertension. 1994;24:301-308.)

Key Words • hypertension, pathology • rats, inbred strains • kidney • arteries • phenotype

In animal models of hypertension, various defects in the kidney that might cause the hypertension have been identified. Thus, in the young Milan hypertensive rat strain, in which blood pressure is close to normal, sodium retention is abnormally high because of an exaggerated reuptake of sodium through an increased Na-K-Cl cotransport activity in the distal tubule. Subsequently, during the maturation process, blood pressure rises, resulting in an increased glomerular filtration rate (GFR) and normalization of sodium homeostasis. In the young spontaneously hypertensive rat (SHR) there is also sodium retention, but it appears to be caused by an increased renal vascular resistance (RVR), a decreased renal plasma flow, and resulting decreased GFR. The increased RVR appears to be caused by narrowing of the renal afferent arterioles, which may be structurally or functionally mediated. Here, the development of hypertension is associated with a normalization of renal plasma flow and GFR and thus, again, normalization of sodium homeostasis. It has been suggested that each of these pathologies may be present in certain forms of human essential hypertension. However, at present there is no prospective evidence even in rat models that any of these pathologies lead to hypertension: current evidence is based on comparison of the hypertensive strains with genetically related normotensive controls, in which differences may be unrelated to the difference in blood pressure.

To obviate this difficulty of using inbred strains, crossbreeding experiments may be used, in which the progeny of a cross between hypertensive and normotensive animals are themselves crossed to produce an F2 generation. The aim is then to determine whether a defect cosegregates with hypertension in the F2 generation animals.
Wistar-Kyoto (WKY) rat population of a phenotypic defect with blood pressure is then evidence of an association of the defect with the pathogenesis of the hypertension. However, used in this manner, the technique cannot determine directly whether the association is due to cause or effect. One way of overcoming this is to analyze the phenotype while the animals are still young and then determine whether the phenotype correlates with later development of high blood pressure. Such longitudinal studies in individuals have not previously been performed.

The present investigation was aimed at testing the hypothesis that a structurally mediated narrowing of the renal afferent arteriole in a young normotensive individual is a cause of subsequent development of hypertension. Experiments were performed using F$_1$ SHR/WKY rats. Afferent arteriolar diameter was measured histologically under standardized conditions in kidneys taken from 7-week-old animals. The uninephrectomized (Nx) animals then continued until age 23 weeks, when steady-state blood pressure was measured intraarterially. The purpose was to determine whether narrow afferent arteriolar diameter at age 7 weeks was a predictor for the development of high blood pressure at age 23 weeks.

**Methods**

**Animals**

The animals used for the experiment were bred in Leicester, UK. Three male SHR were mated with 3 female WKY rats, and 3 male WKY rats were mated with 3 female SHR at the age 12 weeks. These parental SHR were genetically homogenous, as were the parental WKY rats. The resulting F$_1$ generation was again mated at 12 weeks. From the resulting F$_2$ generation, 61 male animals were used for the present investigation. The rats were sent to Aarhus at age 4 to 5 weeks in four groups and were maintained on a normal sodium chow and water ad libitum until the operation.

At age 7 weeks immediately before operation the rats were weighed and systolic blood pressure (SBP$_{7w}$) was measured using the tail-cuff procedure in conscious animals. All procedures performed were in accordance with our institutional guidelines.

**Principle of Method for Determination of Afferent Arteriolar Diameter**

The concept of the method for determination of afferent arteriolar diameter is to allow fixation of the afferent arterioles in situ while they are relaxed and subjected to a transmural pressure of 100 mm Hg. Afferent arteriolar dimensions (lumen diameter and media thickness) are then measured histologically. The principle of the technique has been described previously, but in this experiment, to be able to correlate afferent arteriolar morphology at 7 weeks with arterial blood pressure at 23 weeks, it was necessary to modify the surgical part of the technique to allow the rats to survive the unilateral nephrectomy involved. The surgery will therefore be described in some detail.

**Surgery at 7 Weeks**

Rats were anesthetized with methohexital (Brietal, Eli Lilly & Co; 1%, 7.5 mg/kg body wt IP). After the abdominal wall was opened and the intestines (which constantly were kept moistened) were gently pulled aside, the major arteries were cleaned of fat, and the right kidney was cautiously loosened from underlying connective tissue. The following were then ligated and cut in order: right suprarenal artery, right ureter, and right renal vein. Under a stereomicroscope, the right renal artery was catheterized with a polyethylene tube, and the kidney was perfused with physiological salt solution (PSS, see below) at 100 mm Hg from a suitably elevated bottle in order to wash out the blood. The right renal vein was kept open to allow escape of the perfusate. Immediate and homogenous blanching of the kidney indicated good perfusion. If this was not the case, the rats were excluded (see below). Then, the right kidney (still under pressure) was gently removed from the abdominal cavity to a beaker containing PSS, and the perfusate was changed to plasma solution (human plasma, obtained from a local hospital; 2.50 mg bovine albumin [Sigma Chemical Co] per milliliter of plasma; 0.004 mL heparin per milliliter of plasma; 5000 IU [DAK], at room temperature).

After surgery, the abdominal incision was closed in two layers after injection of antibiotics (Anhpen, ampicillin, Brocades Pharma, 2 mL IP). The wound was covered with adhesive dressing, and the rat was returned to its cage and placed under a heat lamp during recovery. No further medication was given postoperatively. Every fifth rat was sham operated. The abdominal cavity was opened, the organs were slightly manipulated, and antibiotics were given. Afterward, these rats were treated in exactly the same way as the Nx animals.

**Microfil Infusion and Morphometry**

Plasma solution perfusion of the right kidney was continued under 100 mm Hg pressure for 30 minutes. Then the previous procedure was followed. In brief, with perfusion pressure maintained at 100 mm Hg, the vasculature was relaxed by changing the perfusate to a papaverine solution (2 mg papaverine per milliliter of saline, Mecobenzon) for 5 minutes and then to a silicone rubber solution (Microfil, MV-130, Flowtec Ltd) containing ultrasonically dispersed microspheres (latex beads, Sigma [11.9±1.9 μm] [SD], Sigma specification; approximately 200 000 microspheres per milliliter of Microfil) and with the viscosity of plasma for 15 minutes. At this time, flow was decreased greatly mainly because of lodging of the microspheres in the glomerular capillaries. The renal vein was then ligated to stop residual shunt flow through the outer medullary and subcortical zones. This procedure resulted in all vessels containing Microfil being inflated under the same pressure (100 mm Hg) but without hyperfiltration. The Microfil was allowed to harden under these conditions for 2 hours. The kidney was then removed and immersion-fixed in 3% formaldehyde/1% glutaraldehyde in 3/4 Tyrode's buffer for a minimum of 3 days.

The perfused kidneys were split longitudinally into halves. The dorsal half of each kidney was cut into six pieces at right angles to the corticomedullary junction to optimize the number of afferent arterioles cut in cross section. The tissue pieces were preembedded in agar to maintain orientation, dehydrated through a graded series of ethanol solutions, and embedded in glycol methacrylat (Historesin, LKB). Resultant blocks were cut in serial 2-μm-thick sections on a microtome (Reichert-Jung, Supercut 2065), placed on glass slides, stained with Giemsa stain, and coded.

With the use of two microscopes (Olympus, BH2, oil immersion lenses, ×100) equipped with mirrors, pictures of adjacent sections were projected on a tabletop. Inner diameter (ID) and outer diameter (OD, border between media and adventitia) of the vessel were measured with a ruler at a total magnification of ×1650 and a resolution of 0.6 μm. Media thickness and media cross-sectional area were calculated as (OD$_1$−ID$_1$)/2 and π(OD$_2$−ID$_2$)/4, respectively.

We included only vessels that were located in the renal cortex, contained Microfil, had a diameter less than 30 μm, and fulfilled our criteria for being afferent arterioles (see Reference 31). The arterioles were categorized as either distal arterioles, which were observed to be in close relation to the...
TABLE 1. Characteristics of Uninephrectomized and Sham-Operated Rats at 7 and 23 Weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>7 Weeks</th>
<th>23 Weeks</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Nx (n=37)</td>
<td>Sham (n=11)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>154±4</td>
<td>159±7</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, g</td>
<td>208±3</td>
<td>201±6</td>
</tr>
<tr>
<td>Heart/body weight, mg/g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left kidney weight, g</td>
<td></td>
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</table>

N indicates uninephrectomized rats; SBP, systolic blood pressure; and MBP, mean blood pressure. Significance levels by two-tailed Student's t test. n is number of rats. Values are mean±SEM.

Statistics

All results are presented as mean±SEM. Significance of differences between Nx and sham-operated rats (Table 1) and between lowest and highest rat quartiles according to the measured parameters (Tables 3 and 4) were assessed by an unpaired Student's two-tailed t test. Least-squares methods were used for linear regression analyses (Table 2) (STATVIEW statistical package for Macintosh). The null hypothesis that slope and intercept equaled zero was evaluated using Student's t test. Probability levels less than 5% were considered significant.

Results

The protocol for determination of afferent arteriolar diameter at age 7 weeks required uninephrectomy. We therefore included a series of sham-operated animals to ensure that uninephrectomy did not affect rat characteristics at age 23 weeks. As indicated in Table 1, from the same baselines at age 7 weeks, the blood pressures (SBP and MBP), body weights, and ratios of heart weight to body weight were the same in Nx and sham-operated F₂ rats at age 23 weeks. As expected, the only difference was that the remaining kidney was larger in Nx rats than the corresponding kidney in the sham-operated rats.

Table 2 shows the structural parameters measured in the 7-week-old Nx rats of the distal afferent arteriole (lying close to the glomeruli) and the more proximal
arteriole (representing the remainder of the arterioles measured). The r values in Table 2 show the correlation coefficient between each of these 7-week parameters and MBP at 23 weeks (MBP^23-^). A negative correlation was observed for the diameters (both lumen and outer) of the distal afferent arteriole; none of the other parameters (media thickness, media-to-lumen ratio, and media cross-sectional area) correlated with MBP^23-^.

Fig 1 shows the relation between the individual measurements of MBP^23-^ and distal afferent arteriole lumen diameter at 7 weeks (lumen^7-wk^), confirming that a relatively narrow lumen at 7 weeks is associated with a relatively high blood pressure at 23 weeks. This finding is supported by Fig 2, which shows that the percentage increase in SBP between 7 and 23 weeks is also negatively correlated with lumen diameter at 23 weeks. There was no correlation between MBP and the structural parameters of the proximal arterioles.

Quartile analysis on the basis of lumen^7-wk^, which was normally distributed (Fig 3A), was made to determine whether lumen^7-wk^ was associated with increased blood pressure at 23 weeks (Fig 3B). Compared with the rats in the highest lumen^7-wk^ quartile, the rats in the lowest lumen^7-wk^ quartile had (1) a 14% higher SBP at age 23 weeks (Fig 3B), a greater increase in SBP between 7 and 23 weeks (Fig 3C), and a 16% higher MBP^23-^ (Table 3) but a tendency (P=.18) for a lower SBP at age 7 weeks; (2) the same body weight at 7 weeks, but an 11% lower body weight at 23 weeks (Table 3); (3) no difference in right kidney weight at 7 weeks or in left kidney weight at 23 weeks (Table 3); and (4) the same ratio of heart weight to body weight at 23 weeks (Table 3). Furthermore, the relatively small lumen of the distal afferent arterioles at 7 weeks was associated with a larger media-to-lumen ratio but a smaller media cross-sectional area of these vessels (Table 4).

Quartile analysis on the basis of SBP^7-wk^ showed that SBP^7-wk^ was not a predictor of MBP^23-^ for the bottom SBP^7-wk^ quartile: 148 ±6 mm Hg; MBP^23-^ for the top SBP^7-wk^ quartile: 142 ±5 mm Hg). Furthermore, corresponding quartile analyses based on the afferent arteriole structural parameters measured at 7 weeks showed that apart from lumen^7-wk^, none of these parameters were related to MBP^23-^ (confirming the correlation analysis shown in Table 2).

**Discussion**

The main result of this study is that a narrow distal renal afferent arteriole is associated with later development of high blood pressure and that this narrowing appears to be associated with an inhibition of growth. We believe that the present results provide the first direct evidence for a specific renal phenotype playing a role in the chain of events responsible for the etiology of genetically determined hypertension.

**Measurement of Afferent Arteriolar Structure**

The technique we have used differs in a number of important respects from those used by others.15-19,35-36 First, the use of microspheres to lodge in the glomerular capillaries means that the afferent arterioles are fixed...
under a known intravascular pressure. With other perfusion systems, even when fixative is infused at a known pressure, the pressure in the afferent arterioles is not known. Second, the use of Microfil in the perfusate ensures that no filtration occurs, so that interstitial pressure will not rise, and thus transmural pressure during fixation is close to intravascular pressure. Third, the use of papaverine ensures that the vessels are relaxed, whereas with normal perfusion methods, the action of the fixative on the state of activity of the vessels is not known. Fourth, the surgical procedure allows rats to survive the uninephrectomy without affecting the subsequent development of blood pressure (Table 1), thus allowing a longitudinal study. Fifth, the technique allows measurements of both lumen diameter and corresponding media thickness.

Phenotypic Predictors of Hypertension

Previous studies in humans have demonstrated numerous phenotypic differences, including increased peripheral resistance, 37 structurally mediated narrowing of resistance vessels, 37 and alterations in membrane transport (eg, increased Na-K-Cl cotransport 37), but it has not been possible to determine whether these differences are causes or effects of the hypertension. Likewise, in animal studies countless phenotypic differences between genetic hypertensive rats and normotensive controls have been observed, 38 and a small number of these have been shown to correlate with blood pressure in F2 generation animals obtained by crosses between the hypertensive and normotensive animals (eg, increased vascular reactivity 39 and altered resistance artery properties both as regards structure 29 and excitation-contraction 27 30), but, to our knowledge there has been only one study in which F2 animals have been used to ask the question of whether a phenotypic abnormality can predict the development of hypertension. In that study, Harrap and Doyle 32 examined F2 SHR/WKY rats at different ages and showed that although MBP was negatively correlated to GFR in 11-week-old rats, there was no such correlation in 16-week-old rats. Their interpretation was that MBP rose from 11 to 16 weeks in order to normalize GFR, a mechanism that has also been suggested by Arendshorst and colleagues (Arendshorst and Beierwaltes 12 and Dilley et al 13). However, in contrast to the present study, the protocol of those previous studies did not allow individual animals to be followed.

It is important to stress that the phenotypic abnormality seen in our experiments is not a consequence of high blood pressure, for at the time of measurement, blood pressure was not increased in the animals showing the defect (Fig 3B and Table 3). The lack of relation between afferent arteriolar diameter and blood pressure at 7 weeks (Fig 3B) is consistent with young SHR being, at that age, having increased RVR but close to normal blood pressure. 13 14 Thus, it appears that for a period, the rats are having increased RVR but close to normal blood pressure. 13 14 In that study, Harrap and Doyle 13 14 examined F2 SHR/WKY rats at different ages and showed that although MBP was negatively correlated to GFR in 11-week-old rats, there was no such correlation in 16-week-old rats. Their interpretation was that MBP rose from 11 to 16 weeks in order to normalize GFR, a mechanism that has also been suggested by Arendshorst and colleagues (Arendshorst and Beierwaltes 12 and Dilley et al 13). However, in contrast to the present study, the protocol of those previous studies did not allow individual animals to be followed.

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The interpretation that the narrowed afferent arteriolar diameter is the cause of a subsequent increase in blood pressure clearly depends on our confidence that blood pressure was not already increased at age 7 weeks in those animals that subsequently became hypertensive. The measurements at 7 weeks had to be performed by the tail-cuff method rather than intra-arterially because an unacceptably large number of the rats would probably not have been able to survive two operations (uninephrectomy and placement of an aortic catheter) within a short period of time. Nevertheless, we believe

<table>
<thead>
<tr>
<th>Parameter</th>
<th>l_{aa} (n=9)</th>
<th>l_{ap} (n=9)</th>
</tr>
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<tbody>
<tr>
<td>Lumen diameter, μm</td>
<td>12.4±0.1</td>
<td>15.1±0.2*</td>
</tr>
<tr>
<td>Media thickness, μm</td>
<td>3.41±0.14</td>
<td>3.56±0.09</td>
</tr>
<tr>
<td>Media-lumen ratio, %</td>
<td>29.6±1.5</td>
<td>24.7±0.7*</td>
</tr>
<tr>
<td>Media cross-sectional area, μm²</td>
<td>174±8</td>
<td>210±6*</td>
</tr>
</tbody>
</table>

l_{aa} and l_{ap} are mean±SEM for rat quartiles with the smallest and largest lumen diameter of the distal afferent arterioles at 7 weeks of age, respectively. n is number of rats.

*P<.01 by unpaired two-tailed Student's t test.
that the tail-cuff measurements are accurate, for in a previous study, it was found that in our hands tail-cuff and intra-arterial measurements in conscious rats were closely correlated (r = 0.98, n = 12). Moreover, in our hands, the coefficient of variation of tail-cuff measurements is only 7%, and we do not see any change in blood pressure measurements between the first measurement and measurements made over the following 2 weeks. Furthermore, it should be noted that the blood pressure measurements at 7 weeks showed a tendency (P = 0.18) toward a reduced pressure in the rat quartile that subsequently became hypertensive. Therefore, we conclude that blood pressure at 7 weeks was not a predictor of subsequent development of high blood pressure (as also seen previously by Harrap and Doyle in F1 SHR/WKY animals) and that the reduction in average afferent arteriolar diameter at 7 weeks was not related to an already increased blood pressure. It should be emphasized, however, that the predictive value of the measured narrowed afferent arteriolar diameter for later development of high blood pressure is not strong. The correlation coefficient between these two parameters indicates a predictive value of only 13% (r = 0.36, r² = 0.13, Fig 1). However, the cause of hypertension in SHR is polygenic, so high correlation coefficients are not to be expected, even in the absence of measurement error. Nevertheless, the low value of the regression coefficient suggests that afferent arteriolar diameter is but one of the factors involved in the pathogenesis of the disease. The nature of the other factors involved remains to be determined.

Physiological Role for Afferent Arteriolar Diameter

Renal sodium homeostasis is critically dependent on glomerular capillary pressure, which in turn depends on the ratio between postcapillary and precapillary renal resistance. An important controller of this ratio is tubuloglomerular feedback, whereby excess sodium in the distal tubule results in constriction of the afferent arteriole and hence reduction in glomerular pressure and delivery of sodium to the nephron. Disturbance of the ratio through a structurally mediated reduction of afferent arteriolar diameter will therefore result in sodium retention, which in time may be expected, according to the theory of Guyton, to result in a rise in blood pressure in order to normalize sodium homeostasis. A physiological connection between afferent arteriolar diameter and adult blood pressure thus appears likely, a conclusion supported by the finding that specific renal artery dilators cause marked blood pressure reduction. Furthermore, as mentioned above, prospective renal transplantation experiments in rats and retrospective studies of renal transplantsations in humans point to a key role for the kidney in the etiology of hypertension. The present results are therefore consistent with the possibility that lumen <sub>a</sub> is a phenotype that determines blood pressure in SHR.

Cause of Structurally Mediated Narrowing of Afferent Arterioles

As predicted by hemodynamic studies, decreases in lumen diameter and increases in the ratio of media thickness to lumen diameter of resistance vessels in hypertensive individuals have been documented both in humans and animals. Originally, it had been thought that this could be caused by an encroachment of the media into the lumen and thus be due to vascular growth. However, evidence now exists that the increased media-to-lumen ratio is not due to growth but more to an alternative arrangement of the same amount of material around the narrower lumen, a process known as remodeling. This is consistent with the present study, in which the rats with the reduced lumen of the distal afferent arterioles had an increased distal artery media-to-lumen ratio even though these arteries did not show growth. Indeed, the media cross-sectional area (equal to media volume per unit length) of these arteries was reduced. This therefore raises the possibility that the cause of the reduced lumen is a lack of growth of the vessels, i.e., that restricted growth prevents the lumen of the vessels from developing in the normal manner. Thus, it could be that growth inhibition in the afferent arterioles is a determinant of subsequent development of hypertension.

The clear implication of our longitudinal study is that one or more of the genetic determinants that influence blood pressure in the SHR do so by influencing the size of the renal afferent arteriole. Sometimes, the distribution profile of the phenotype in the F1 population can help to ascertain whether the trait is determined by a single genetic locus. In our case, the normal distribution of the values for lumen <sub>a</sub> (Fig 3A) suggests polygenic influences, although the number of animals studied was small, and one cannot reliably exclude an important effect of a single gene. Of potential relevance is that loci for a number of renally expressed genes (renin and SA) have already been shown to cosegregate with increased blood pressure in crosses involving the SHR. The mechanisms by which these loci influence blood pressure remain to be determined. It is worth noting, however, that there is evidence that treatment of young SHR with an angiotensin-converting enzyme inhibitor reverses the abnormalities in renal hemodynamics and attenuates the development of later hypertension.

Relevance to Essential Hypertension

As mentioned above, there is some retrospective evidence that the kidney plays a key role in the development of essential hypertension, as it does in most animal models of hypertension. The underlying renal mechanisms are not known. Even though increased RVR is reported in the offspring of parents with essential hypertension, it is most unlikely that early narrowing of the renal afferent arteriole occurs in all forms of essential hypertension. Other studies find no average difference in RVR, whereas Cusi and Bianchi have identified a subgroup with increased RVR and shown that these have abnormal Na-K cotransport. However, it has been suggested that the similarities seen between SHR and the “nonmodulator” group of human essential hypertensive patients (those with a blunted renal blood flow response to salt load) indicate that the SHR may be a relevant model for this particular patient group. On this basis, it may be speculated that also in humans a narrowed renal afferent arteriole at a young age is associated with the later development of high blood pressure.
In conclusion, we have demonstrated that a narrowed distal afferent arteriole in young F344 SHR/WKY rats is associated with later development of high blood pressure in these animals. It appears that the narrowed lumen is a result of an inhibition of arteriolar growth. However, further investigations are required to determine the mechanisms underlying this abnormality.

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