Elevated Renovascular Tone in Young Spontaneously Hypertensive Rats
Role of Cytochrome P-450

John D. Imig, John R. Falck, Debebe Gebremedhin, David R. Harder, Richard J. Roman

The present study examined the role of cytochrome P-450 metabolites of arachidonic acid in elevating renal vascular resistance in young spontaneously hypertensive rats (SHR). Differences in vascular tone were assessed in the preglomerular vasculature of 3- to 4-week-old prehypertensive SHR (n=11) and normotensive Wistar-Kyoto (WKY, n=10) and Wistar-Lewis (n=10) rats. Pressure-diameter relations to changes in renal perfusion pressure were compared using the juxtamedullary nephron microvascular preparation perfused in vitro with a physiological salt solution. At a pressure of 60 mm Hg, the basal diameters of the interlobular arteries and proximal and distal afferent arterioles of the SHR averaged 43±2, 17±0.3, and 11±0.4 μm, respectively. The diameters of the interlobular arteries and afferent arterioles were 9% to 14% smaller than those of corresponding vessels in WKY and Wistar-Lewis rats. Addition of P-450 inhibitors, ketoconazole (100 μmol/L) or 7-ethoxyresorufin (1 μmol/L), to the perfusate dilated the afferent arteriole of SHR by 7% to 12%, whereas it increased the diameter by only 0% to 6% in control rats and significantly reduced the differences in the pressure-diameter relation in the preglomerular vasculature of SHR and control rats. Inhibitors of P-450 eliminated the contractile response of afferent arterioles to increases in renal perfusion pressure in all three groups. Removal of calcium from the perfusate eliminated differences in the diameters of the preglomerular vasculature in SHR and normotensive rats. Renal P-450 activities in SHR and normotensive rats were compared by incubating cortical microsomes with [14C] arachidonic acid, and the products were separated by reversed-phase high-performance liquid chromatography. The production of the primary metabolite, 20-hydroxyeicosatetraenoic acid, was significantly greater in SHR than in WKY rats, whereas the production of 11,12-epoxyeicosatrienoic acid was greater in WKY rats than in SHR and Wistar-Lewis rats. These observations indicate that cytochrome P-450 metabolites of arachidonic acid enhance preglomerular vascular tone in juxtamedullary nephrons of young SHR, which may contribute to the resetting of the pressure-natriuretic relation. (Hypertension. 1993;22:357-364.)

KEY WORDS • cytochrome P-450 • kidney • hemodynamics • hypertension, renovascular • vascular resistance

P revious studies have indicated that the relation between arterial pressure and sodium excretion is shifted toward higher pressures before the development of hypertension in both spontaneously hypertensive rats (SHR) and Dahl salt-sensitive rats. In the SHR, the blunted pressure-natriuretic response is associated with a reduction in papillary blood flow and renal interstitial hydrostatic pressure. Recent studies by Gebremedhin et al suggest that the decline in papillary blood flow in adult SHR is due to an enhanced vascular tone rather than structural changes in the preglomerular vasculature of the deep nephrons. However, little is known about the renal vasculature of very young SHR, and it remains to be determined if changes in renal vascular reactivity occur very early in the development of hypertension.

The factors responsible for elevating renal vascular tone in SHR are unknown. The recent findings that the expression of the cytochrome P-450 IVA2 gene and the renal production of 20-hydroxyeicosatetraenoic acid (20-HETE) are elevated in young SHR suggest that this system may be involved. This view is further supported by the observation that administration of heme arginate or SnCl₂, which lowers renal cytochrome P-450 activity, reduces arterial pressure in SHR. However, the mechanisms by which P-450 metabolites of arachidonic acid alter arterial pressure, renal function, or both are unknown. Recently, we have reported that cytochrome P-450 metabolites of arachidonic acid are produced by the renal microcirculation and that these compounds play a role in the myogenic response of renal arterioles to elevations in transmural pressure. The purpose of the present study was to determine whether enhanced vascular tone occurs in the renal preglomerular vasculature of young SHR and to determine the possible contribution of cytochrome P-450 metabolites of arachidonic acid to the elevation in renal medullary vascular resistance previously observed in these animals.
Methods

Measurement of Arterial Pressure

Experiments were performed on 4-week-old SHR (88±5 g body weight) and Wistar-Kyoto (WKY) rats (102±4 g body weight) and Wistar-Lewis rats (98±4 g body weight) purchased from Harlan Sprague Dawley, Inc, Madison, Wis. The rats were housed in an animal care facility at the Medical College of Wisconsin approved by the American Association for Accreditation of Laboratory Animal Care and had free access to food and water throughout the study. All protocols involving animals were approved by the Animal Care Committee of the Medical College of Wisconsin. The rats were anesthetized with ketamine (25 mg/kg) and xylazine (1 mg/kg), and a catheter was implanted in the femoral artery for measurement of arterial pressure. The catheter was exteriorized at the back of the neck and brought out through a stainless-steel spring and swivel device. After a 2-day recovery period, arterial pressure was directly measured with a pressure transducer and recorded for 0.5 to 1.0 hour per day on 3 consecutive days while the animal was conscious with free movement in its cage. Heart rate and systolic, diastolic, and mean arterial pressures were determined and reduced to a single mean value for the entire recording period.

Pressure-Diameter Studies

These experiments were performed on 3- to 4-week-old SHR (70±5 g body weight), WKY (73±4 g body weight), and Wistar-Lewis (72±5 g body weight) rats. The renal vasculature of the Wistar-Lewis strain was studied to provide a second normotensive inbred control rat strain to compare with the SHR because of the evidence for genetic heterogeneity in the WKY rat and its questionable adequacy as a control. The rats were anesthetized with pentobarbital (65 mg/kg body wt), and a catheter was implanted in the femoral artery and exteriorized at the back of the neck and brought out through a stainless-steel spring and swivel device. After a 2-day recovery period, arterial pressure was directly measured with a pressure transducer and recorded for 0.5 to 1.0 hour per day on 3 consecutive days while the animal was conscious with free movement in its cage. Heart rate and systolic, diastolic, and mean arterial pressures were determined and reduced to a single mean value for the entire recording period.

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Assessment of Renal Cytochrome P-450-Dependent Metabolism of Arachidonic Acid

Previous studies have indicated that there are differences in cytochrome P-450 metabolism in young SHR vs WKY rats. However, we felt it necessary to compare P-450 metabolism in young SHR, WKY, and Wistar-Lewis rats because of the previously documented genetic differences in WKY rats obtained from different suppliers and questions regarding the adequacy of WKY rats as the sole normotensive control strain for SHR. In addition, P-450 metabolism is dependent on age, sex, diet, and other environmental factors; therefore,
Therefore, we felt it important to study P-450 metabolism of arachidonic acid in the same three groups of rats that were used in our renal microcirculatory studies. In these experiments, 3- to 4-week-old SHR, WKY, and Wistar-Lewis rats were anesthetized with pentobarbital (65 mg/kg body wt IP). The kidneys were removed via laparotomy and placed in an ice-cold 0.9% sodium chloride solution. The renal cortex and outer medulla were dissected and homogenized in ice-cold 0.9% sodium chloride solution. The renal cortex and outer medulla were dissected and homogenized in ice-cold potassium phosphate buffer (10 mmol/L, pH 7.7) containing 250 mmol/L sucrose, 1 mmol/L EDTA, and 0.1 mmol/L phenylmethylsulfonyl fluoride (PMSF). Renal microsomes were prepared by differential centrifugation to obtain microsomal pellets as previously described. The microsomes were suspended in potassium phosphate buffer (0.1 mol/L, pH 7.4) containing 10 mmol/L MgCl$_2$, 1 mmol/L EDTA, 1 mmol/L NADPH, and an NADPH-regenerating system (20 mmol/L isocitrate and 0.1 U/mL isocitrate dehydrogenase). Control incubations were also performed without NADPH to test for the possible nonenzymatic metabolism of arachidonic acid. After 30 minutes, the reaction was terminated by acidification to pH 4.5 with 0.1 mol/L formic acid and extracted twice with 3 mL ethyl acetate. The combined organic phase was back extracted with 1 mL distilled water to remove residual acid. The extracts were evaporated to dryness under N$_2$ and reconstituted in 500 μL ethanol.

Metabolites were separated with a 2 mm x 25 cm C18 reversed-phase high-performance liquid chromatography.
graphic column and a linear solvent gradient ranging from acetonitrile/water/acetic acid (50/50/0.1, vol/vol/vol) to acetonitrile/acetic acid (100/0.1) over 40 minutes. The arachidonic acid metabolites were monitored with an on-line radioactive flow detector (Flo-one/Beta, series A-120, Radiomatic Instruments, Tampa, Fla). The effects of cytochrome P-450 inhibitors on the metabolism of arachidonic acid by renal cortical microsomes of SHR, WKY, and Wistar-Lewis rats were studied. In these experiments, microsomes were assayed as described above under control conditions and after preincubation of the microsomes with 7-ER (1 μmol/L) in the presence of 1 mmol/L NADPH for 30 minutes or ketoconazole (100 μmol/L) for 15 minutes.

Statistics

Data are presented as mean±SEM. The significance of differences of mean values between groups was evaluated with two-way analysis of variance for repeated measures followed by a Duncan’s multiple range test. One-way analysis of variance followed by the Bonferroni test was used to determine the significance of differences in mean arterial pressure and cytochrome P-450 metabolite production rates between the groups. A value of \( P<.05 \) was considered to be statistically significant.

Results

Measurement of Arterial Pressure

Mean arterial pressure averaged 126±2 mm Hg in conscious 4-week-old SHR (n=9) and 113±4 mm Hg in WKY (n=7) and 103±3 mm Hg in Wistar-Lewis (n=6) rats. SHR had a significantly (\( P<.05 \)) elevated mean arterial pressure compared with WKY and Wistar-Lewis rats.

Pressure-Diameter Studies

Fig 1 summarizes the effects of cytochrome P-450 inhibitors and calcium-free media on pressure-diameter relation of distal afferent arterioles of Wistar-Kyoto (WKY) rats (n=10 rats; n=15 vessels), Wistar-Lewis (Lewis) rats (n=10 rats; n=20 vessels), and spontaneously hypertensive rats (SHR) (n=11 rats; n=22 vessels). Pressure-diameter relations were measured under control conditions (left) and 30 minutes after addition of ketoconazole (100 μmol/L) or 7-ethoxyresorufin (1 μmol/L) to the perfusate (middle). Pressure-diameter relations after removal of calcium from bath and perfusate are presented in the right panel. *Significant difference from control value in same rat strain; †significant difference from corresponding value measured in WKY and Wistar-Lewis rats; ‡significant difference from corresponding value measured in WKY and SHR rats; §significant difference from corresponding value in SHR and Wistar-Lewis rats; ||significant difference from value measured at 60 mm Hg in the same group.

Fig 3. Line graphs show effect of cytochrome P-450 (P450) inhibitors and calcium-free media on pressure-diameter relation of distal afferent arterioles. Under control conditions (Fig 1, left), the diameter of the interlobular artery of the SHR was significantly smaller than the corresponding vessels measured in WKY and Wistar-Lewis rats. The diameters of the interlobular arteries decreased by 4% in the WKY rats and SHR but did not change significantly in Wistar-Lewis rats when perfusion pressure was elevated from 60 to 120 mm Hg. Addition of the P-450 inhibitors to the perfusate had no effect on the basal diameter (Fig 1, middle) of the interlobular arteries (measured at 60 mm Hg), but it did alter the response of the interlobular artery from a slight decrease to a significant 5% increase in diameter when perfusion pressure was elevated from 60 to 120 mm Hg in SHR and Wistar-Lewis rats. Removal of calcium from the bath and perfusate (Fig 1, right) further dilated the interlobular arteries in SHR and Wistar-Lewis rats. WKY rats exhibited the least amount of active vascular tone under control conditions, as the basal diameter of the interlobular artery increased by only 2% in calcium-free media. Wistar-Lewis rats exhibited an intermediate degree of active vascular tone as the interlobular artery diameter increased by 8%, and SHR exhibited the greatest amount of vascular tone as the basal diameter of the interlobular artery increased by 13%. The differences in the pressure-diameter relation between SHR and WKY rats were completely eliminated by removal of calcium from the medium, and the passive diameter of the interlobular artery was greater in the Wistar-Lewis than in the WKY rats or SHR.

The results comparing the pressure-diameter relations of the proximal afferent arterioles in SHR and normotensive rats are presented in Fig 2. The basal diameters of the proximal afferent arteriole in SHR were smaller than corresponding diameters observed in WKY and Wistar-Lewis rats by 9% and 8%, respectively (Fig 2, left). The proximal portion of the afferent arterioles exhibited similar significant reductions (4% to
7%) in diameter in all three groups when pressure was elevated from 60 to 120 mm Hg. Addition of P-450 inhibitors to the perfusate increased the basal diameter of the proximal afferent arteriole by 7% in SHR (Fig 2, middle). In contrast, the diameter of the proximal afferent arteriole in WKY and Wistar-Lewis rats increased by only 0% and 2%, respectively. Inhibitors of P-450 eliminated the differences in the pressure-diameter relations of the proximal afferent arterioles in SHR and normotensive rats. In all three groups, administration of the P-450 inhibitors completely eliminated the vasoconstrictor response of the proximal afferent arteriole to elevations in perfusion pressure. Calcium-free media further increased the basal diameters and eliminated differences in the pressure-diameter relations of the proximal afferent arteriole in all three groups (Fig 2, right). Similar to the results obtained in the interlobular artery, the SHR had a much larger active tone in the afferent arteriole than the normotensive rats.

The effects of cytochrome P-450 inhibitors and calcium-free media on the pressure-diameter relations of the distal afferent arteriole in SHR and normotensive rats are presented in Fig 3. Under control conditions, the basal diameters of the distal afferent arterioles in SHR were smaller than corresponding diameters observed in WKY and Wistar-Lewis rats by 8% and 16%, respectively (Fig 3, left). Elevation of perfusion pressure from 60 to 120 mm Hg reduced the diameter of the afferent arterioles in all three groups. Addition of cytochrome P-450 inhibitors to the perfusate significantly increased the basal diameters of the distal afferent arterioles of SHR and Wistar-Lewis rats (Fig 3, middle) and had no effect on the diameters of these vessels in WKY rats. Inhibitors of P-450 partially eliminated the differences in the pressure-diameter relations between SHR and WKY rats; however, the SHR diameter remained smaller than that of the Wistar-Lewis rats after addition of P-450 inhibitors. In all three groups, administration of the P-450 inhibitors greatly attenuated the vasoconstrictor response of the distal afferent arteriole to elevations in perfusion pressure. Calcium-free media increased the distal afferent arteriole diameters in all three groups, and there was no significant difference in the pressure-diameter relations between SHR and Wistar-Lewis rats (Fig 3, right). Again, the WKY rats had the least amount of active tone, and the passive diameter of the distal afferent arteriole of the WKY was smaller than that of the SHR and Wistar-Lewis rats.

In a separate group of experiments, the influences of ketoconazole and 7-ER on the vasoconstrictor response to norepinephrine and the vasodilator response to acetylcholine on the renal cortical microvessels were examined. Inhibition of cytochrome P-450 activity had no effect on either the vasoconstrictor response to norepinephrine or on the relaxant response to acetylcholine. Norepinephrine reduced the diameter of renal microvessels by 19.8±2.9% before and 16.2±3.3% (n=11 vessels) and 18.4±2.2% (n=10) after treatment with ketoconazole and 7-ER, respectively. Similarly, acetylcholine increased vascular diameters by 27.4±5.3% before and by 25.6±3.2% (n=11) and 31.5±5.9% (n=10), respectively, after inhibition of renal P-450 activity with ketoconazole and 7-ER.
involved. The present study examined whether changes in renal vascular tone are apparent early in the development of hypertension in young SHR and evaluated the potential contribution of P-450 metabolites of arachidonic acid to the altered vascular tone in these animals.

In the present study we examined the preglomerular vasculature in young SHR. We found that the internal diameters of the interlobular artery and proximal and distal portions of the afferent arterioles of juxtamedullary glomeruli were significantly smaller in young SHR than the diameters of corresponding vessels inagematched WKY and Wistar-Lewis rats at all perfusion pressures studied. In SHR, removal of calcium from the perfusion and superfusion solutions dilated the entire preglomerular vasculature to a greater extent in SHR than in normotensive rats and eliminated the differences in the pressure-diameter relations between SHR and normotensive rats. These results indicate that the smaller diameters of the renal preglomerular vasculature of young SHR vs normotensive rats are due to differences in active vascular tone rather than a structural narrowing of the vessels. Previous studies have demonstrated an increased cerebral vascular tone in young SHR,19 and studies of the skeletal muscle microcirculation have shown an increased vascular resistance20-22 that was due, in part, to vascular rarefaction.22 The present study is the first to observe directly an increase in active renal vascular tone as early as 4 weeks in the SHR. Our observations are consistent with previous reports indicating that renal vascular resistance and vascular reactivity to vasoconstrictors are elevated in young SHR23-25 and that these differences occur before the development of major structural changes in the renal vasculature.26

Previous studies have indicated that the pressure-natriuretic response is altered in young SHR and that this is associated with a reduction in papillary blood flow.3 The present findings suggest that an elevated vascular tone in the preglomerular vasculature of juxtamedullary nephrons of SHR may account for the elevated renal medullary vascular resistance in this model. The elevated vascular tone in the preglomerular vasculature would be expected to lower pressures in the vasa recta circulation and reduce renal medullary interstitial hydrostatic pressure, a major determinant of the pressure-natriuretic response. These changes in medullary hemodynamics and renal interstitial hydrostatic pres-

**FIG 4.** Representative reversed-phase high-performance liquid chromatography chromatograms of cytochrome P-450 metabolites of arachidonic acid after incubation of renal cortical microsomes of spontaneously hypertensive rats (SHR, top) and Wistar-Kyoto (WKY) rats (bottom) with $[^{14}C]$arachidonic acid (AA) (30-minute peak). Peaks that eluted at 8.5 and 9.5 minutes have the same retention times as those of 14,15- and 11,12-dihydroxyicosatrienoic acids (dHETE). Peaks that eluted at 11, 17.5, and 19 minutes coeluted with 20-hydroxyeicosatetraenoic acid (20-HETE) and 14,15- and 11,12-epoxyeicosatrienoic acids (EET), respectively. Total number of counts was similar in the chromatograms: 58 051 cpm for SHR and 56 345 cpm for WKY rats.
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HETE, 20-hydroxyeicosatetraenoic acid; EETs, epoxyeicosatrienoic acids; DIHETEs, dihydroxyeicosatrienoic acids.

FIG 5. Bar graph shows comparison of production of cytochrome P-450 metabolites of [14C]arachidonic acid by renal cortical microsomes of young spontaneously hypertensive rats (SHR, n=6), Wistar-Lewis (Lewis) rats (n=6), and Wistar-Kyoto (WKY, n=7) rats. *Significant difference from corresponding production rate in WKY rats; 20-HETE, 20-hydroxyeicosatetraenoic acid; 11,12-EET, 11,12-epoxyeicosatrienoic acid; 11,12-DIHETE, 11,12-dihydroxyeicosatrienoic acid.

FIG 6. Bar graph shows effect of ketoconazole (KETO, 100 μmol/L) and 7-ethoxyresorufin (7ER, 1 μmol/L) on metabolism of [14C]arachidonic acid by renal cortical microsomes of spontaneously hypertensive rats (SHR) (KETO, n=4; 7ER, n=3), Wistar-Lewis (Lewis) rats (KETO, n=4; 7ER, n=3), and Wistar-Kyoto (WKY) rats (KETO, n=4; 7ER, n=3). 20 HETE, 20-hydroxyeicosatetraenoic acid; EETs, epoxyeicosatrienoic acids; DIHETEs, dihydroxyeicosatrienoic acids.

sure would require an elevated perfusion pressure to normalize the pressure-natriuretic relation in young SHR. Thus, the elevated mean arterial pressure observed in young SHR may be required to normalize papillary blood flow and renal interstitial hydrostatic pressure and to maintain sodium balance.

The factors responsible for elevating vascular tone in the kidney of SHR are unknown. Presumably, this must be a local factor because our observations were made in an in vitro preparation. In the present study, cytochrome P-450 inhibitors produced a greater dilation in the afferent arteriole of SHR than in normotensive rats and partially eliminated the differences in pressure-diameter relations in the preglomerular vasculature of normotensive and hypertensive rats. These results indicate that P-450 metabolites of arachidonic acid contribute to the elevated vascular tone of young SHR.

Cytochrome P-450 inhibitors also attenuated the pressure-dependent vasoconstriction of the afferent arterioles in all groups. This observation is consistent with the results of a recent study indicating that arachidonic acid potentiates and P-450 inhibitors block the myogenic response of isolated perfused dog renal arteries to elevations in transmural pressure. Our present findings also suggest that cytochrome P-450 metabolites of arachidonic acid may participate in renal autoregulatory responses of the afferent arteriole of rats to changes in perfusion pressure.

To determine the P-450 metabolites of arachidonic acid that could possibly contribute to the alterations in renal vascular tone in SHR, we compared the metabolism of arachidonic acid in renal cortical microsomes of SHR and normotensive rats. We confirmed previous findings that 20-HETE is the major P-450 metabolite of arachidonic acid produced by renal cortical microsomes and that the production of this metabolite is increased in young SHR compared with WKY rats. In previous studies we found that isolated dog renal arteries can synthesize 20-HETE and that 20-HETE is a potent vasoconstrictor of renal arteries. More recently, we have found that 20-HETE has a dose-related vasodilator effect on preglomerular vessels in the juxtamedullary nephron preparation. Thus, it is possible that the enhanced production of 20-HETE in SHR may be involved in elevating renal vascular tone particularly in the deep nephrons, lowering papillary blood flow and resetting the pressure-natriuresis relation previously observed in these animals. This mechanism is consistent with previous observations that the expression of the P-450 IVA2 gene and P-450 ω-hydroxylase activity is elevated before development of hypertension in young SHR. It also provides a mechanism to explain how administration of SnCl2 to induce heme oxygenase and lower renal P-450 activity might promote sodium excretion at lower levels of pressure and prevent the development of hypertension.

We also observed large differences in the production of 11,12-EET and 11,12-DIHETE between SHR and WKY rats. 11,12-EET is a vasodilator and 11,12-DIHETE is a less active breakdown product; this shift from EETs to DIHETEs could possibly contribute to the differences in vascular tone observed. The renal vascular effects of these substances and how they may contribute to the differences in vascular tone between SHR and WKY rats remain to be determined.

Because of the molecular evidence of genetic heterogeneity in the normotensive WKY rat, it may not be an adequate control strain for the SHR. Therefore, we also compared diameters of the preglomerular vasculature in SHR with those observed in a second normotensive inbred rat strain. SHR rats exhibit an enhanced preglomerular renal vascular tone compared with Wistar-Lewis rats. In addition, the differences in pressure-diameter relations between SHR and Wistar-Lewis rats, like WKY rats, are partially eliminated by cytochrome P-450 inhibitors, indicating that P-450 metabolites contribute to the differences in renal vascular tone between these strains. In contrast to WKY rats, the metabolism of arachidonic acid by cytochrome P-450 in renal cortical microsomes is not significantly different between SHR and Wistar-Lewis rats. These observations suggest that differences in the responsiveness of the renal vasculature to 20-HETE and other P-450 fatty acid metabolites rather than differences in...
metabolite levels may contribute to the differences in vascular tone in SHR and Wistar-Lewis rats. In contrast, both an increased production of 20-HETE as well as an enhanced responsiveness to a P-450 metabolite may contribute to the differences observed between SHR and WKY rats. Supporting this concept is the observation that cytochrome P-450 inhibition had the largest dilator effect on the preglomerular vasculature of SHR, an intermediate effect on that of Wistar-Lewis rats, and a very small effect on WKY preglomerular basal vascular diameters.

In summary, the present results suggest that active preglomerular vascular tone in deep nephrons is elevated in young SHR. The production of the renal metabolites may contribute to the differences observed between SHR and WKY rats. Supporting this concept is the observation that cytochrome P-450 inhibition had the largest dilator effect on the preglomerular vasculature of SHR, an intermediate effect on that of Wistar-Lewis rats, and a very small effect on WKY preglomerular basal vascular diameters.

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