Structural Vascular Changes in Hypertension
Role of Angiotensin II, Dietary Sodium Supplementation, Blood Pressure, and Time

Geza Simon, Gyorgy Illyes, Botond Csiky

Abstract—The dose and time dependence of angiotensin II (Ang II)–induced hypertension and structural vascular changes and the effect of dietary sodium supplementation on these relationships were investigated. Male Sprague-Dawley rats were treated with 50, 100, or 200 ng · kg⁻¹ · min⁻¹ Ang II subcutaneously for 4 or 12 weeks on normal sodium diet (0.7% NaCl) or with 50 ng · kg⁻¹ · min⁻¹ Ang II SC for 12 weeks on high sodium diet (2% NaCl). Additional rats were sham-operated and fed normal sodium (control rats) or high sodium diet. Plasma Ang II level of rats receiving 100 ng · kg⁻¹ · min⁻¹ Ang II for 4 weeks was 26±2 pg/mL (mean±SEM, n=7) compared with 11±2 pg/mL (n=15) in control rats (P<0.03). Lumen and external diameters of small (50 to 100 μm OD) and intermediate-size (100 to 150 μm OD) resistance arteries were measured in maximally dilated, pump-perfused (55 to 60 mm Hg), in situ fixed mesenteric vascular beds of rats, and wall-to-lumen ratios (W/L) were calculated. Large mesenteric arteries of rats treated with 100 ng · kg⁻¹ · min⁻¹ Ang II for 12 weeks were examined to distinguish hypertrophy from hyperplasia of vascular muscle. Tail systolic blood pressure (BP) and W/L of resistance arteries of Ang II–treated rats increased in a dose-dependent manner. Treatment with 50 ng · kg⁻¹ · min⁻¹ Ang II for 12 weeks had no significant effect on BP but produced the same increase in W/L (+10%, n=8, P<0.06) as 100 ng · kg⁻¹ · min⁻¹ Ang II for 4 weeks (+9%, n=18, P<0.05) (time dependence). A 2% NaCl diet for 12 weeks had no significant effect on either BP or W/L, but in combination with 50 ng · kg⁻¹ · min⁻¹ Ang II, it increased systolic BP by 31 mm Hg (P<0.01) and W/L of small resistance arteries by 28% (P<0.01) (synergism). In rats treated with 100 ng · kg⁻¹ · min⁻¹ Ang II for 12 weeks, arterial smooth muscle cell thickness was increased without a change in the number of cell layers (hypertrophy). There was a dissociation between the average BP load (the area under the weekly systolic BP curve) of Ang II–treated rats and the W/L of their mesenteric resistance arteries. Ang II–induced hypertension and structural vascular changes are dose- and time-dependent and synergistically enhanced by dietary sodium supplementation. Dissociation between BP and vascular structure in Ang II–treated rats suggests that a direct trophic effect of Ang II may contribute to the development of structural vascular changes. (Hypertension. 1998;32:654-660.)

Key Words: arteries | morphometry | mesenteric circulation

The long-term administration of initially subpressor doses of angiotensin II (Ang II) to rats mimics the development of human renovascular and high-renin (Ang II) essential hypertension. The onset of hypertension is preceded by a prehypertensive period characterized by trophic stimulation of vascular muscle and potentiation of pressor and vasoconstrictor responses to Ang II itself (autopotention). This is followed by the onset of hypertension and the development of structural vascular changes. Preliminary data in our laboratory indicated that this orderly process is both dose- and time-dependent. By time dependence we mean the phenomenon whereby one half of an effective dose of Ang II may take twice as long as the full dose or longer to produce hypertension and structural vascular changes. This is an important concept because it suggests that a stimulus that is undetectable at any one point in time, when applied long enough, may lead to hypertension. The first aim of this investigation was to provide experimental data for the dose and time dependence of Ang II–induced hypertension.

The second aim of this investigation was to explore the relationship between the onset of hypertension and the development of structural vascular changes in Ang II–treated rats. Structural vascular changes are the hallmark of chronic hypertension, and increased wall-to-lumen ratio (W/L) of resistance arteries is the predominant lesion. The increase in relative “thickness” of resistance arteries is responsible for the “amplifier” property of the arterial circulation in hypertension, which functionally manifests itself as pressor or vasoconstrictor hyperresponsiveness. Whether structural vascular changes are primary or secondary to blood pressure (BP) elevation remains an unsettled issue. In the majority of studies of hypertension, there has been a direct relationship
between BP and W/L of arteries, but discrepancies also exist. In some experimental models, there is hypertension without structural vascular changes, or structural vascular changes are modest in magnitude despite severe hypertension. Certain strains of rats are more prone to develop structural vascular changes than other strains. Other studies have raised the question of whether a trophic stimulus alone may be sufficient to induce structural vascular changes and thereby initiate the hypertensive process. Ang II has been a prime candidate for such a role. These findings suggest that BP is not the sole determinant of structural vascular changes. In the present study, therefore, a dissociation was sought between the extent of Ang II–induced hypertension and the W/L of resistance arteries as evidence that mechanisms other than the level of BP play a role in the pathogenesis of structural vascular changes. Finally, because dietary sodium supplementation potentiates both the vasoconstrictor and vascular trophic action of Ang II, we also investigated the effect of high sodium diet on the rate of onset and extent of hypertension and structural vascular changes in Ang II–treated rats.

Methods

Design of Experiments

Pathogen-free male Sprague-Dawley rats (Sasco, Omaha, Neb) on a normal sodium (0.7% NaCl) diet were used throughout these studies. Male rats were investigated to eliminate the changes in the renin-angiotensin system that accompany the estrous cycle in female rats. At the beginning of the experiments, the rats weighed 400 to 450 g. Young adult rats were chosen because Ang II treatment may influence the growth of rats independently of its pressor effect. Ang II was administered to rats in three different doses (50, 100, and 200 ng · kg⁻¹ · min⁻¹) for 4 or 12 weeks to test the hypothesis that the agonist exerts a dose- and time-dependent effect on the development of hypertension and of structural vascular changes. Additional rats received high sodium (2% NaCl) diet alone or in combination with 50 ng · kg⁻¹ · min⁻¹ Ang II for 12 weeks to test for a synergistic effect of the 2 stimuli. It has been estimated that 2% NaCl diet of rats corresponds to daily intake of ~15 g of salt by humans, a salt load that sometimes is encountered in clinical practice. A 2% NaCl diet by itself was not expected to produce hypertension in Sprague-Dawley rats. Sham-operated rats on normal sodium diet for 4 or 12 weeks served as controls for all the treatment groups, including the rats on high sodium diet.

Preparation of Rats

Alza model 2 ML4 (28-day) minipumps implanted subcutaneously were used to deliver Ang II for 4 weeks. To deliver Ang II for 12 weeks, the empty minipumps were surgically removed at weeks 4 and 8, and new ones were implanted. Procedures for the filling and implantation of the minipumps have been previously reported. The dose of Ang II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe; Sigma Chemical Co) was 50, 100, or 200 ng · kg⁻¹ · min⁻¹ SC based on the body weight of rats at the time of the implantation of the first minipump. Control rats and rats on high sodium diet were fitted with empty restroilerized minipumps to reduce costs. The rate of delivery of the 4-week minipump is 2.5 μL/h; in previous experiments, we found that the delivery of this volume of vehicle (0.01 N acetic acid) to control rats had no detectable metabolic or hemodynamic effect. The rats had free access to tap water and received either normal (0.7% NaCl) or sodium-supplemented (2% NaCl) diet. The diets were matched for other ingredients, including potassium (200 mmol/kg). The diets were prepared on order by Harlan Teklad.

Tail Systolic BP Measurements

Systolic BP was measured in restrained awake rats by the tail-cuff method (Narco Biosystems) between 8 and 11 AM. Measurements were made on at least 2 occasions before the insertion of the first minipump to rule out spontaneous hypertension (SBP >130 mm Hg). Rats whose SBP exceeded 130 mm Hg were rejected from the study. After insertion of the first minipump, the SBP of rats was measured weekly for 4 weeks and then every 2 weeks for the rest of the experiment. The BP load that rats were exposed to during the experiments was calculated as the area under the SBP curve. The area was calculated by subdividing the BP curve of each rat into weekly or biweekly trapezoids, by computing the area of each trapezoid, and, finally, by adding up the calculated areas. The rats were weighed to the nearest 1 g on the day of the final experiments.

Intra-Arterial BP Measurements

For direct measurement of BP, rats were fitted with a femoral artery catheter 7 to 10 days before the end of the 4- or 12-week treatment period. The operation was performed in pentobarbital (45 mg/kg IP)-anesthetized rats. Through a skin incision in the left groin, a polyvinyl chloride catheter was advanced into the abdominal aorta through the femoral artery and fixed in place. The distal end of the catheter was tunneled subcutaneously with the aid of a trocar from the groin to the back of the neck, where it was exteriorized through a puncture wound. Postoperatively, the rats received acetaminophen for analgesia in their drinking water (1.5 mg/mL) for 1 day. After a 3-day recovery period, the arterial catheter was connected to a pressure transducer (Kent Scientific Corp), and the mean arterial BP (MAP) was monitored continuously for 2 hours between 8 AM and 12 PM on 3 separate days. During monitoring, rats moved freely in their boxes. The filtered analog signals were digitized with a Maclab analog/digital converter and sampled using an Apple computer with system 7 software. The average MAP was calculated from collected data for each day, and the average daily MAP during 3 days of measurement was calculated.

At the completion of direct BP measurements, arterial blood samples were obtained from 7 awake rats receiving 100 ng · kg⁻¹ · min⁻¹ Ang II SC and from 15 control rats. Plasma Ang II concentrations (pg/mL) were measured in Dr Ben Zimmerman’s laboratory (Department of Pharmacology, University of Minnesota) using high-performance liquid chromatography fractionation and radioimmunoassay.

In Situ Tissue Fixation

The techniques used for the in situ fixation of the mesenteric and left renal vascular bed of rats have been previously reported. Briefly, the rats were anesthetized with 75 mg/kg chloralose IV and allowed to breathe spontaneously through a tracheostomy tube. After systemic anticoagulation (1000 U IV) and vasodilatation (500 μg papaverine IV per rat), the mesenteric and left renal circulation of rats was pumped-perfused retrogradely through the abdominal aorta with aerated (5% CO₂, 95% O₂) Krebs-Ringer bicarbonate solution at 37°C, to which 75 μg/mL papaverine was added. The inferior vena cava was cut open to allow free circulation of the perfusate through the left kidney and the mesentry. Perfusion pressure in the aorta was adjusted to 55 to 60 mm Hg and kept constant by adjusting the pump flow rate for the rest of the infusion period. The pressure range of 55 to 60 mm Hg was chosen because we have found previously that after maximal systemic vasodilatation, MAP falls to this level in rats treated with Ang II and in control rats. The mesenteric and left renal vascular beds were perfused sequentially with Krebs-Ringer solution for 8 to 10 minutes, with fixative containing 2.5% glutaraldehyde, 1.8% sucrose, and 0.063 mol/L phosphate buffer (pH 7.4, 400 mOsm) for 15 minutes, and with 0.200 mol/L phosphate buffer for 8 to 10 minutes. At the end of perfusion, the left kidney and the entire small intestine and mesenteric vascular arcade were removed for further processing.
Morphometric Measurements

For the purposes of this study, morphometric measurements were restricted to mesenteric arteries. The small intestine was cut into 2- to 3-cm segments, each segment retaining its own vascular arcade, and post-fixed in 10% buffered formalin. A wooden stick was inserted into the lumen of the intestinal segments to straighten the junction of the intestinal wall and the vascular arcade where the cuts for histological sections were going to be made. Three to four intestinal segments were dehydrated through graded series of ethanol and were infiltrated with and embedded in paraffin. Cuts were made at a right angle and parallel to the mesenteric intestinal junction; this resulted in cross-sectional cuts of small mesenteric arteries. Sections of 4 μm thickness were stained with hematoxylin and eosin, which delineated the outer media and adventitia. Two criteria were used to select arteries for morphometric measurements. First, by inspection, the thickness of the vessel wall had to be uniform throughout its circumference. Second, only vessels with a long-to-short axis ratio of <1.50 were measured. In the present study, 2 categories of resistance arteries, 1 with external diameter of 50 to 100 μm (small) and the other with external diameter of 100 to 150 μm (intermediate-size), were investigated. Morphometric measurements of external and lumen diameters along the long and short axes of cross-sectionally cut arteries were obtained under ×450 magnification with a calibrated filar micrometer. Measurement of external diameter extended from the margin of the outer media to the margin of the outer media of the opposing wall. The 2 measurements of external and lumen diameters were averaged. The observer (G.S.) was blinded as to the treatment that the rats received. Measurements were made on a minimum of 3 cross-sectionally cut arteries in each of the 2 vessel categories investigated (see above). Wall thickness and W/L and the mean of each parameter were calculated for the 2 categories of vessels for each rat.

For further characterization of structural vascular changes induced by Ang II treatment, four 2nd-order mesenteric arteries (250 to 350 μm OD) were removed from each of nine rats treated with 100 ng · kg⁻¹ · min⁻¹ Ang II for 12 weeks and from seven 12-week control rats. The arteries were cleaned of adhering tissue, dehydrated through graded series of ethanol, and embedded in epoxy resin. Cross sections of 1 μm thickness were stained with toluidine blue. Arterial segments sectioned tangentially (nonuniform thickness of the vessel wall) were discarded. A video camera (Cell Analysis Systems Inc) connected to an image analysis processor (NIH Image 1.54, Public Domain Software) and microcomputer was used to measure lumen diameter, wall thickness (from endothelium to outer media), the number of smooth muscle cell layers, and cell thickness. The latter 3 parameters were measured at 4 points where arbitrarily drawn horizontal and vertical axes intersected the vessel wall. Cell thickness was measured at the midpoint of the nucleus along the short axis of the smooth muscle cell. Measurements obtained from 2 to 4 arteries per rat were averaged. W/L was calculated.

Statistical Analysis

Results

By inspection, all rats remained healthy to the end of the study. The body weight of rats undergoing 4 weeks of treatment was as follows: controls, 497±25 g (n=8); and rats treated with 50, 100, and 200 ng · kg⁻¹ · min⁻¹ Ang II, 547±18 (n=6), 486±7 (n=22), and 474±9 (n=8) g, respectively. In the 12-week treatment groups, the body weight was as follows: controls, 514±24 g (n=7); rats treated with 50 and 100 ng · kg⁻¹ · min⁻¹ Ang II, 534±26 (n=8) and 598±17 g (n=9, P<0.01 compared with controls), respectively; rats treated with 50 ng · kg⁻¹ · min⁻¹ Ang II and fed 2% NaCl, 467±27 g (n=6); and rats fed 2% NaCl, 520±22 g (n=17). The tail SBP of rats is shown in Figures 1 and 2. There was rapid development of severe hypertension in rats receiving intermediate-size arteries followed by preplanned contrasts (Superanova). To compare the dimensions of large arteries of rats treated with 100 ng · kg⁻¹ · min⁻¹ Ang II for 12 weeks and of matched control rats, the 2-factor ANOVA was extended to include the large arteries. In Ang II–treated rats, the contribution of dose and duration of treatment to changes in W/L was tested with 2-factor ANOVA (factor 1, dose; factor 2, 4 or 12 weeks of treatment). For this analysis, only rats on a normal sodium diet (0.7% NaCl) receiving 50, 100, or 200 ng · kg⁻¹ · min⁻¹ Ang II for 4 or 12 weeks were included. One-way ANOVA was used to compare plasma Ang II concentrations in rats receiving 100 ng · kg⁻¹ · min⁻¹ Ang II SC for 4 weeks with those of control rats. Null hypotheses were rejected at P<0.05.
200 ng · kg⁻¹ · min⁻¹ Ang II SC for 4 weeks. Because of the severe hypertension that developed in these rats, 12-week treatment of rats with this dose of Ang II was not attempted. The development of hypertension was more gradual in rats treated with the 100 ng · kg⁻¹ · min⁻¹ dose of Ang II, reaching moderate levels by ≈4 weeks of treatment. In rats treated with 50 ng · kg⁻¹ · min⁻¹ Ang II, BP rose transiently at 3 and 4 weeks but returned to baseline by the end of the 12-week treatment period (Figures 1 and 2). (This may have been due to weight gain of rats that resulted in a diminishing dose of Ang II per kilogram of body weight as the experiments progressed.) During the 12-week treatment, the BP of rats treated with 50 ng · kg⁻¹ · min⁻¹ was not different from that of control rats. The BP curve of control rats and of rats receiving the 2% NaCl diet overlapped during the entire treatment period. However, when the 2% NaCl diet was combined with the administration of 50 ng · kg⁻¹ · min⁻¹ Ang II, SBP of rats began to rise by week 3, reaching mildly elevated levels by week 12. At the end of 4 weeks of treatment, the plasma Ang II level of rats receiving 100 ng · kg⁻¹ · min⁻¹ Ang II SC (26±5 pg/mL, n=7) was increased compared with that of control rats (11±2 pg/mL, n=15) (P<0.03).

The W/Ls of small and intermediate-size mesenteric resistance arteries of rats in the various treatment groups are summarized in Figures 3 and 4. A dose-dependent increase in the W/L of both categories of vessels was observed, but the increases were generally greater in small arteries. The increase in the W/L of small arteries of rats treated with 50 ng · kg⁻¹ · min⁻¹ Ang II for 12 weeks was of borderline statistical significance (P<0.06) (Figure 3). The effect of dose and time of administration of Ang II on W/L was analyzed by 2-factor ANOVA (see above). In the small arteries, there was a significant independent effect of dose of Ang II (P<0.01) but not of duration of treatment (P>0.20) on wall thickening (Figure 3). In intermediate-size arteries, the effect of both dose and duration of treatment was statistically significant (P<0.02 and P<0.01, respectively) (Figure 4).

Like the increase in W/L of small arteries of rats treated with 50 ng · kg⁻¹ · min⁻¹ Ang II for 12 weeks, the increase in W/L of small arteries of rats treated with 2% NaCl diet for 12 weeks was of borderline statistical significance (P<0.07). Interestingly, 9 of the 17 rats displayed an increase in W/L (10.7%, mean), whereas the remaining 8 rats had no response at all (W/L=8.5%, mean). When the 2% NaCl diet of rats was combined with the administration of 50 ng · kg⁻¹ · min⁻¹ Ang II for 12 weeks, a highly significant increase in W/L was achieved (synergism).

Vessel dimensions of rats treated with 100 ng · kg⁻¹ · min⁻¹ Ang II and of control rats are shown in the Table. For reasons stated in Methods, statistical comparison of small and intermediate-size artery dimensions in Ang II–treated and

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control rats was confined to that of W/Ls. W/L of both categories of arteries was increased in Ang II–treated rats. Statistical comparison of large-artery dimensions in the 2 groups revealed increased wall thickness, W/L, and vascular smooth muscle cell thickness in Ang II–treated rats without a change in the number of smooth muscle cell layers. This finding indicates vascular muscle hypertrophy rather than hyperplasia. Arterial wall hypertrophy in Ang II–treated rats is illustrated in Figure 5.

A high degree of correlation was found between directly measured MAP and the average weekly tail SBP of rats (Figure 6). This finding indicated that the latter was an acceptable measure of the BP load of rats. This permitted us to construct the final summary figure (Figure 7) on which the W/Ls of small arteries of the various treatment groups are plotted against their average BP load, calculated as the area under the SBP curves of rats (Figures 1 and 2) (see Methods). Included in Figure 7 are the results from a previous study in which neonatally sympathectomized adult male rats were treated with 200 ng·kg⁻¹·min⁻¹ Ang II SC for 4 weeks or sham-treated (control). The figure illustrates that there is a dissociation between the BP load that these rats were exposed to and the W/L of their small mesenteric arteries, especially in the earliest stages of hypertension. This impression was confirmed by linear regression analysis of the BP load and W/L of small mesenteric arteries of individual rats that were treated with Ang II for 4 weeks (r=0.15, n=32, NS) or for 12 weeks (r=0.04, n=23). Rats fed a 2% NaCl for 12 weeks were not included in this analysis. A similar dissociation was found between the BP load of rats and the W/L of their intermediate-size mesenteric arteries (data not shown).

Discussion

The findings of this study provide evidence for dose and time dependence of Ang II–induced hypertension and of the
concomitant development of structural vascular changes. A lesser dose of Ang II may lead to the same increase in W/L of resistance arteries as a higher dose as long as the period of treatment is increased. Subthreshold or near-threshold stimuli, such as 2% NaCl diet and 50 ng·kg⁻¹·min⁻¹ Ang II SC, applied simultaneously lead to hypertension and the development of structural vascular changes, demonstrating true synergism. When the W/L of resistance arteries and the BP load over time of several groups of Ang II–treated rats were plotted together on the same graph, a clear dissociation between structural vascular changes and BP was demonstrated, especially in the earliest stages of hypertension.

Previously, we have investigated small and large mesenteric artery structure in rats treated with various doses of Ang II for 6 weeks. We found that the earliest changes were detectable in the smallest arteries (50 to 100 μm OD), some of which may be best characterized as arterioles. Because of methodological problems, morphometric measurements seldom have been performed on these arteries. Therefore, their importance in the development of hypertension may have been overlooked. Neonatal sympathectomy had a different importance in the development of hypertension may have been performed on these arteries. Therefore, their importance in the development of hypertension may have been overlooked. Neonatal sympathectomy had a different importance in the development of hypertension may have been performed on these arteries. Therefore, their importance in the development of hypertension may have been overlooked. Neonatal sympathectomy had a different importance in the development of hypertension may have been performed on these arteries.

Very interestingly, in the present study, there was also a trend for increased W/L of small resistance arteries in salt-fed rats. This was achieved with moderate salt supplementation that resulted mainly from elevation of BP and sympathetic stimulation.
The nature and development of structural vascular changes have been the focus of numerous investigations into the pathogenesis of hypertension because without these changes chronic hypertension does not occur.4,7 Increased W/L of arteries is the predominant lesion; it may result from increased vessel wall area (hypertrophy or hyperplasia of vascular muscle) or from reduced lumen due to restructuring of elements of the vessel wall (remodeling).6,8 In genetic forms of experimental and human hypertension, the primary pathological alteration appears to be remodeling.4 In contrast, in the nongenetic models of hypertension, medial hypertrophy seems to predominate.4,7 In the only study (beside our own) in which structural vascular changes have been investigated in an Ang II–induced model of hypertension, the increase in W/L of large mesenteric arteries was due almost entirely to cellular hypertrophy.21 The present study confirms this finding. In the same-size arteries that were investigated by Griffin et al,21 we found vascular smooth muscle cell hypertrophy without evidence for hyperplasia. The importance of the present study lies in the analysis of the relationship that exists between BP and structural vascular changes in this model of hypertension. When BP load over time and W/L of small resistance arteries of the various treated groups of rats were plotted on the same graph, a clear dissociation between the 2 parameters was observed in the earliest stages of the hypertensive process. It appears that this is the time to investigate the relationship between pressure and structure in hypertension. The dissociation between BP load and vascular structure in the earliest stages of hypertension suggests that a direct trophic effect of Ang II, in addition to its pressor one, is contributing to the development of structural vascular changes. Further meticulous studies in the early stages of hypertension are needed to confirm these observations.

In summary, the development of structural vascular changes in Ang II–treated rats is dose- and time-dependent. The earliest changes are detected in small resistance arteries and in arterioles. The dissociation between BP load and W/L of mesenteric resistance arteries in the earliest stages of hypertension suggests that direct trophic stimulation of vascular wall by Ang II contributes to the development of structural vascular changes. Dietary sodium supplementation potentiates the trophic vascular and pressor effect of Ang II. The administration of small, initially subpressor doses of Ang II to rats for a long period of time promises to be a useful model for the development of human essential hypertension.

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References
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