PDGF-A expression correlates with blood pressure and remodeling in 1K1C hypertensive rat arteries

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Dobrian, Anca, Suzanne S. Wade, and Russell L. Prewitt. PDGF-A expression correlates with blood pressure and remodeling in 1K1C hypertensive rat arteries. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H2159–H2167, 1999.—We previously demonstrated remodeling of large and small arteries in angiotensin II-treated rats, paralleled by an increased expression of platelet-derived growth factor (PDGF)-A chain mRNA in large arteries. Both remodeling and PDGF-A expression were associated with elevation of blood pressure rather than a direct effect of angiotensin II. To further delineate the role of PDGF-A and elevated blood pressure, we assessed the level of PDGF-A and -B mRNA and protein in the wall of large as well as small arteries in the one-kidney, one-clip (1K1C) hypertensive rat, a non-renin-dependent model of hypertension. Fourteen days after renal artery stenosis, the thoracic aorta and both femoral arteries were collected from 1K1C rats (n = 8) and uninephrectomized controls (n = 8) and immediately processed for morphological measurement, immunohistochemistry, RT-PCR, and Western blotting. Systolic blood pressure was significantly elevated in hypertensive rats (202 ± 26 mmHg) compared with control rats (122 ± 7.9 mmHg) and was accompanied by arterial hypertrophy in both aorta and femoral arteries. The mRNA for PDGF-A chain was increased threefold in the thoracic aorta (P < 0.05) of 1K1C rats, whereas the message for PDGF-B was not significantly changed in hypertensive versus control animals. A higher staining of the intima-media layer was observed by using an anti-PDGF-A-chain monoclonal antibody on paraffin-embedded sections. Western blot results indicated an ~2-fold increase in PDGF-A protein in aortic and femoral wall of the 1K1C rats. The results showed that both the mRNA and protein for PDGF-A chain are increased and well correlated with the blood pressure and wall area, suggesting a direct effect of elevated pressure on PDGF synthesis, which, in turn, may affect the onset and progression of vascular hypertrophy.

Hypertension; aorta; femoral artery; platelet-derived growth factors; hypertrophy

Hypertension is accompanied by vascular changes that vary according to the size and structure of each particular artery. These changes include the hypertrophy of large arteries (27, 41) and the inward eutrophic remodeling of arterioles (13, 28), whereas small arteries (internal diameter 150–250 µm) may undergo inward eutrophic or hypertrophic remodeling, depending on the type of hypertension (12, 16). The exact mechanisms and the factors affecting these vascular changes are only known in part. Lately, the involvement of growth factors in the processes of vascular growth and remodeling has been emphasized. Among them, platelet-derived growth factor (PDGF) is of special interest for the autocrine regulation of protein synthesis (9) and growth (7) in smooth muscle cells. Large vessels from normotensive rats and humans constitute express low levels of PDGF-A mRNA, mainly in the medial layer, whereas the PDGF-B chain mRNA is primarily found in the adventitia (3, 36). Also, smooth muscle cells isolated from thoracic aortas of newborn and adult rats constitutively express PDGF-A message (33, 36).

There are data showing enhanced expression of PDGF-A chain mRNA in thoracic aorta of spontaneously hypertensive rats (26), hypertensive Sprague-Dawley rats (23), and angiotensin-treated Wistar rats (42). However, there is no unanimous opinion on the exact stimulus responsible for the enhanced PDGF-A expression in hypertension. On the basis of in vivo experiments, Majeski et al. (23) concluded that PDGF-A expression is induced by α1-adrenergic stimulation, whereas other studies suggest that angiotensin II may be the stimulus that induces PDGF-A expression (25, 42). Another candidate is elevated pressure, which may be a stimulus for vascular hypertrophy (21, 38) as well as for PDGF expression (29, 41). Studies with smooth muscle cells in culture indicate that mechanical strain may enhance PDGF-A and PDGF-B mRNA expression and protein synthesis (43). A recent report (39) also shows that cyclic strain may increase the expression of PDGF-B mRNA in cultured endothelial cells. A previous study (29) from our laboratory indicates that arterial hypertrophy and enhanced PDGF-A expression from angiotensin II infusion occurs in response to elevated arterial pressure rather than as a direct effect of angiotensin II. Thus increased expression of PDGF-A in the vascular wall has been shown in response to a variety of stimuli that suggest it could be important in hypertensive arterial remodeling. A non-renin-dependent model of experimental hypertension that exhibits arterial remodeling similar to that seen in human essential hypertension (1, 35) is the one-kidney, one-clip (1K1C) hypertensive rat (13, 30). We used this model to examine the correlation among blood pressure levels, arterial remodeling, and PDGF expression and secretion in the arterial wall of large- and small-sized arteries.

MATERIALS AND METHODS

Treatment groups. The institutional Animal Care and Use Committee approved procedures involving animals. Male Wistar rats (6–8 wk, 145–180 g; Harlan Sprague Dawley, Indianapolis, IN) were randomly divided into two groups: uninephrectomized controls (n = 8) and 1K1C hypertensives.
(n = 8). All rats were anesthetized with a single injection of ketamine hydrochloride (80 mg/kg ip) and xylazine (12 mg/kg). The 1K1C group of rats was made hypertensive by application of a silver clip with a 230-μm gap width (5) on the left renal artery followed by removal of the right kidney. Control rats were also uninephrectomized, and the left renal artery was isolated in the same manner as in 1K1C rats but without applying a clip. We injected the rats with penicillin G (25,000 U im) before the surgery to prevent the risk of infection. The animals were housed two per cage, given regular rat chow and tap water ad libitum, and maintained on a 12:12-h light-dark cycle during the experiment.

Systolic blood pressures. The onset and further development of hypertension was assessed by measuring the indirect systolic tail-cuff blood pressures with a Narco Biosystems Electro-Sphygmomanometer (Houston, TX) after warming the rats at 35°C for 5 min, under slight restraint. For each rat, blood pressure was measured under conscious conditions every 3 days, beginning the day before surgery and continuing until the end of the experiment. The average of three pressure readings was recorded for each measurement.

Tissue preparation. Fourteen days after surgery, the rats were anesthetized with pentobarbital sodium (60 mg/kg). To measure the mean blood pressure, the tail artery was cannulated (PE-10) and 0.1 ml/100 g (1,000 U/ml) of heparin were injected intra-arterially. The blood pressure was measured with a brush transducer and model 2200 recorder (Gould, Cleveland, OH). After decapitation and exsanguination, the thoracic aorta and both femoral arteries were harvested and immediately processed for further analysis. One segment of each vessel was fixed in methyl Carnoy’s fixative and embedded in paraffin for immunocytochemistry and morphometric analysis, one piece was processed for mRNA extraction, and one piece was quickly frozen in acetone on dry ice and used for Western blotting.

Morphological analysis. Thin sections (5 μm thick) of the paraffin-embedded tissue were dehydrated and stained for 1 min with toluidine blue to visualize the intima-media of the vessel wall. The internal and external circumferences of each vessel were measured using a video-based image system with edge-tracking software (J. AVA., Jandel Scientific). The mean of three different measurements was used to calculate the internal and external diameters and the intimal-medial area.

RNA isolation and RT-PCR. Freshly excised pieces of aortic and femoral arteries were immediately homogenized in Trizol Reagent (GIBCO-Life Technologies, Grand Island, NY) and subjected to total RNA isolation, according to an improved one-step method that was initially developed by Chomczynski and Sacchi (8). The total RNA was frozen at −80°C and further reverse transcribed and amplified within the next 3 mo. The RT-PCR reaction was performed using the GeneAmp E Z Tth RNA PCR kit (Perkin Elmer, Foster City, CA). Typically, each RNA was reverse transcribed at 60°C for 20 min using gene-specific primers and the resulting cDNA was amplified in the same tube by using a 0.4 μM concentration of the primer pairs for either PDGF-A, PDGF-B, or GAPDH as the reference housekeeping gene. The primers for rat PDGF-A and PDGF-B were published sequences (11, 19), whereas primers for GAPDH were designed using the sequences from GenBank and PCCGene Software. All primers were purchased from GibCO BRL. The following rat sequences were used as primers: 1) PDGF- AA: 5′-AAGCATGTGGCGGGAAGACGC-3′, 5′-TCTCCTAACTCCACCTGGGAC-3′; 2) PDGF-BB: 5′-GAAGCCAGTCTTCAC-3′, 5′-AAGGTCCACCGGATTGAGGTGT-3′; and 3) GAPDH: 5′-CAACGGATTTTGCGATTGCC-3′, 5′-CCATTCTCAGCTTTGACTTGCC-3′. Preliminary experiments were performed to establish the linearity range for each PCR reaction and the optimal annealing temperatures. In all cases after the RT step the templates were heated at 94°C for 30 s, annealed for another 30 s, and finally subjected to a 72°C extension for 1 min. The PCR reaction for PDGF-A was performed at an annealing temperature of 58°C for 26 cycles in thoracic aorta and for 27 cycles in femoral arteries. RNA was also amplified using the PDGF-B primers for 35 cycles at a 45°C annealing temperature. The reaction for GAPDH was performed each time in similar conditions as for the respective growth factors. The PCR products were electrophoresed on an 8% polyacrylamide gel and stained with ethidium bromide, and the intensity of the bands was measured by densitometry using an EagleEye System (Stratagene) and SigmaGel Software (Jandel Scientific). The results are expressed as the ratio (mean ± SD) of growth factor mRNA to GAPDH mRNA.

Immunohistochemistry for PDGF-AA. Pieces (length 1–4 mm) of either thoracic aorta or femoral arteries were fixed in methyl Carnoy’s solution (60% methanol-30% chloroform-10% acetic acid) for 4 h and then paraffin embedded. Sections were deparaffinized in xylene and rehydrated in graded ethanols. Endogenous peroxidase was blocked by incubation in 3% hydrogen peroxide in cold methanol, and nonspecific binding was blocked by incubation in 5% normal goat serum in PBS supplemented with 1% BSA. The sections were then incubated with a polyclonal rabbit anti-human PDGF-AA antibody (Genzyme Diagnostics) that recognizes both human and rat (24, 34) PDGF-A chain (in the form of both AA and AB dimers) and demonstrates <10% reactivity with PDGF-BB. The primary antibody was used at a 1:100 dilution in 1% BSA-PBS overnight at 4°C in a humid chamber. After successive washings in PBS and BSA-PBS between each incubation, the slides were reacted with biotinylated secondary goat anti-rabbit antibody (1:500 dilution) (Vector Laboratories, Burlingame, CA), the ABC-Elite avidin reagent (Vector Laboratories), and finally with the ImmunoPure Metal Enhanced DAB Substrate kit (Pierce, Rockford, IL) as the chromogen. The sections were counterstained with Gill’s hematoxylin, dehydrated, and coverslipped. In control experiments, the primary antibody was replaced with blocking solution (5% normal goat serum and 1% BSA). No immunostaining was observed under this condition. Immunoblotting studies, which were conducted by incubating the primary antibody with excess human recombinant PDGF-AA (1:10) (Genzyme Diagnostics) for 2 h, also resulted in an absence of immunostaining. Results were quantified by counting the stained cells under a light microscope at ×200 magnification. Five different areas for each artery were counted (≈1,000 cells), and the results were averaged and expressed as the percentage (mean ± SD) of stained cells out of the total cell number.

Western blotting for PDGF-AA. After the removal of the adventitial layer under the microscope, pieces of the aorta and femoral arteries were freeze-dried in acetone on dry ice for several hours and then weighed, thawed, and further homogenized in a Tris-HCl buffer (pH 6.8) containing 1 mM EDTA, 1% SDS, 10% glycerol, 50 mM NaF, 10 μg/ml Leupeptin, 20 μg/ml aproatin, and 1 mM PMSF (final concentrations). The homogenates were left on ice for 1 h and centrifuged at 4°C at 10,000 g for 20 min. Protein content was assayed according to the bichioronic acid method (37) using a Sigma kit (Sigma, St. Louis, MO). All aliquots containing 30 μg of protein were separated by gel electrophoresis (as described by Laemmli, Ref. 18). Nonreducing conditions and 10% polyacrylamide gels were used for studies of PDGF-AA. Proteins were then electrophoretically transferred to Nytran membranes (Amersham Life Science) (40).
Nonspecific binding was blocked by incubation with 5% dried milk in 0.1% Tween 20 in TBS for 1 h at room temperature. The blots were then reacted with polyclonal human anti-rabbit PDGF-A (Santa Cruz Biotechnology), which specifically recognizes only the PDGF-AA homodimer both in humans and rats (2). The incubation took place for 2 h at room temperature with a 1:250 diluted antibody. After extensive washings in TWEEN-TBS, the blots were incubated with horseradish peroxidase-labeled secondary goat anti-rabbit antibody (Amersham Life Science) at a 1:4,000 dilution, for 1 h at room temperature. After the final washings, the blots were incubated with an ECL kit (Amersham Life Science) and exposed each time for precisely 5 min to Hyperfilm ECL. The bands corresponding to PDGF-AA were quantified using densitometry (SigmaGel, Jandel Scientific), and the results were expressed as arbitrary units of intensity, normalized to milligrams of extracted tissue protein. In control experiments, PDGF-AA protein (recombinant human, Santa Cruz Biotechnology) was used to demonstrate specificity of the antisera. As a negative control, the primary antibody was replaced by normal rabbit IgG at an equivalent dilution.

Statistical analysis. All data were analyzed for statistical significance by ANOVA for repeated measures and by Student's t-test. The null hypothesis was rejected at P < 0.05.

RESULTS

Systolic blood pressures as measured by the tail-cuff method were significantly elevated above control levels in 1K1C rats starting from day 3 after the surgery until the day of death (Fig. 1). Mean arterial blood pressures measured under anesthesia, through an indwelling catheter in the tail artery, indicated a significant increase in the 1K1C rats (132.8 ± 6.9 mmHg) compared with control rats (77.3 ± 6.4 mmHg; P < 0.001). Body weight of 1K1C rats (292.2 ± 17 g) was not significantly different from that of control rats (288.8 ± 19.2 g) at the conclusion of the 14-day experimental period.

Cross-sectional wall area of both the thoracic aorta and femoral artery was significantly elevated (P < 0.01) in 1K1C rats versus controls (Fig. 2, A and B). This increase was accompanied by an enlargement of the lumen, expressed as internal diameter, which was significantly higher in hypertensive rats for the thoracic aorta but not for the femoral arteries (Fig. 2, A and B). Wall-to-lumen ratios for thoracic aorta of 1K1C (0.103 ± 0.03) and controls (0.094 ± 0.01) were not significantly different (P = 0.44) because both the lumen and wall thickness increased in the hypertensive group. For the same reason, femoral wall-to-lumen ratios did not differ significantly between 1K1C and control rats (0.37 ± 0.16 vs. 0.45 ± 0.15, respectively). These results suggest that both central and peripheral arteries undergo outward, hypertrophic remodeling in this model of hypertension. Blood pressure and wall thickness were highly correlated in the thoracic aorta (r = 0.90) and to a lesser extent in the femoral artery (r = 0.65) (Fig. 2, C and D).

We used RT-PCR to determine the expression of PDGF-A and PDGF-B in hypertrophied versus normal arteries, and we compared the ratio between the mRNA of each of the two growth factors and GAPDH mRNA as the internal control. The results indicated no significant difference in PDGF-B expression in thoracic aorta and femoral arteries of hypertensive animals versus controls. In the thoracic aorta the ratio of PDGF-B to GAPDH was 0.26 ± 0.15 in the 1K1C group and 0.32 ± 0.15 in the control group. In femoral arteries the ratio was 0.15 ± 0.1 for the 1K1C group and 0.22 ± 0.16 for the control group. In contrast, PDGF-A expression was increased threefold in 1K1C thoracic aorta and 1.8-fold in femoral arteries compared with controls; however, this difference was statistically significant in the thoracic aorta only (Figs. 3 and 4). However, wall area, as an index of hypertrophy, correlates well with PDGF-A expression in both the thoracic aorta (r = 0.77) and the femoral artery (r = 0.62) (Fig. 4, B and C). These results indicate that vascular remodeling in hypertensive animals is paralleled by an increased expression of PDGF-A but not PDGF-B mRNA especially in large arteries such as the thoracic aorta.

On the basis of these results, we further identified and quantified the secreted PDGF-AA protein in the vascular wall. The presence and distribution of PDGF-A chain protein in the form of both -AA and -AB dimers was accomplished by immunohistochemistry on paraffin-embedded tissues, previously fixed in methyl Carnoy's fixative. The staining was uneven in the thoracic aorta of the control animals, being present mostly in the intima and the adjacent smooth muscle cells (Fig. 5B). Some staining was also present in the adventitial layer, but most of it was probably nonspecific, because it was also seen in the method control where primary antibody was omitted (Fig. 5A). In the hypertrophied...
arteries of 1K1C rats, the aortic staining was more uniformly distributed in the media and the endothelial layer (Fig. 5C). There was also an enhanced staining of the adventitial layer compared with normal arteries. The method control shows no staining in the media (Fig. 5A). In the control femoral arteries, PDGF-A immunostaining was occasionally found, mostly in the medial layer and, to a lesser extent, in the adventitia (Fig. 5E). In hypertensive animals, the staining was more pronounced both in media and adventitia (Fig. 5F), although the adventitial staining is partly nonspecific, as shown by the method control samples (Fig. 5D).

The same pattern of distribution was observed in all specimens tested, albeit the intensity of the staining slightly varied with each specimen. The staining seemed to be specific because the replication of the immunohistochemical procedures with absorbed recombinant PDGF-A peptide removed the staining identified with the anti-PDGF-A antibody (not shown). The counting of the stained cells in the intima and media showed a significant difference between the hypertensive and control animals in both thoracic aorta and femoral arteries (Fig. 6).

To confirm and better quantify these results, we performed a Western blot analysis of tissue extracts from both hypertensive and control animals. Strongly staining bands were observed at ~31 kDa, when the gels were run under nonreducing conditions (Fig. 7). In the thoracic aorta of hypertensive animals there was a 2.2-fold increase in the PDGF-AA protein homodimer compared with the control animals (Fig. 7). For most of the animals the same elevated expression of protein was also observed in the femoral arteries (Fig. 7). For some of the gels, a sample containing purified PDGF-AA was also blotted and reacted with the antibody, and a single band was observed at 32 kDa. When the first
antibody was omitted, only nonspecific staining corresponding to high-molecular-weight proteins was observed (data not shown). When the X-ray films were quantitated by densitometry and the results normalized to milligrams of extracted protein, the differences between the hypertensive and control rats were statistically significant for both thoracic aorta and femoral arteries (Fig. 8A). The amount of secreted PDGF-AA homodimer strongly correlated with wall area of the thoracic aorta \((r = 0.78)\) (Fig. 8B) and femoral artery \((r = 0.64)\) (Fig. 8C).

**DISCUSSION**

The present study demonstrates that PDGF-A chain mRNA and protein levels are increased in hypertrophic aorta and femoral arteries of 1K1C hypertensive rats and that PDGF-A expression and secretion in the media are correlated with both blood pressure and vascular hypertrophy. It was recently demonstrated in hypertensive angiotensin II-treated rats that increased PDGF-A expression and arterial hypertrophy were associated with elevated blood pressure rather than a direct effect of angiotensin II (29). The 1K1C model of rat hypertension is known to provide highly reproducible elevations in blood pressure independently of the renin-angiotensin system after the first 3 to 6 days (6, 10, 13). Moreover, the plasma renin activity 2 wk after surgery is not increased in hypertensive animals compared with controls (15). Therefore, in this particular model, blood pressure, and not angiotensin, seems to be the main stimulus that induces PDGF-A upregulation and vascular hypertrophy.

The results show that both thoracic aorta and femoral artery undergo hypertrophy, because the wall area was significantly increased in hypertensive animals (Fig. 2). It was previously demonstrated that this type of remodeling is characteristic of large arteries in hypertension (29, 41), whereas inward, eutrophic remodeling is characteristic of small arteries and arterioles (13, 28). In our case, the hypertrophy of both types of arteries was well correlated with blood pressure, confirming previous results showing that pressure is one of the main stimuli to induce arterial wall hypertrophy in 1K1C rats (41).

The presence of PDGF-A chain mRNA found in the aortic wall of control animals (Fig. 7) is in accordance to previous studies performed on rat and human vessels, indicating that they constitutively express small amounts of PDGF-A mRNA and protein (3, 36). We found that in hypertensive vessels the mRNA for PDGF-A chain is increased threefold, and its expression correlates well with both blood pressure and wall area, the latter being an index of hypertrophy. Several studies have emphasized the role that PDGF-A may play in the remodeling of the arterial wall in hypertension. Increased PDGF-A expression has been found in aortas of spontaneously hypertensive rats (SHR) and angiotensin-treated rats (26, 42). Moreover, the treatment of SHR with antisense oligonucleotides for PDGF-A significantly reduced hypertrophy of the thoracic aorta, without altering blood pressure (11). On the other hand, neither PDGF-A nor -B seems to be upregulated in the DOCA-salt model of hypertension (32), suggesting that other mediators of vascular hypertrophy must exist and high levels of DOCA may suppress expression of PDGF-A.

In this study, we show that in addition to the thoracic aorta, femoral arteries of hypertensive animals also undergo hypertrophy accompanied by elevated PDGF-A mRNA and protein levels. Therefore, PDGF-A seems to have a role in hypertrophy of smooth muscle cells in a more muscular peripheral artery, suggesting that there
may be a common mechanism involved in the development of hypertrophy of the arterial wall in different types of arteries.

PDGF-B mRNA was found at low levels in control arteries, and the level exhibited a trend, although not statistically significant, toward lower levels in both thoracic aorta and femoral arteries of hypertensive animals. Although some authors (3) have shown that PDGF-B is expressed only in the adventitia of the vascular wall and not in the intima or media, more recent studies (24, 32) have shown low levels of PDGF-B mRNA in the media of rat aorta and carotid arteries. The data of Lindner and Reidy (20) indicate that neither form of PDGF is found in endothelial cells until after injury. Our data may suggest that PDGF-A and -B are independently regulated in smooth muscle cells during hypertrophy of the arterial wall. It was shown that PDGF-A and -B chains may be transcriptionally regulated through 5′-untranslated GC-rich sequences (31) or posttranscriptionally regulated through mRNA stability in addition to splicing of primary transcripts (4). Independently regulated expression of PDGF-A and -B transcripts has been reported previously for smooth muscle cells (17, 22) and other cell types (14, 17). Further investigation is needed to explain the exact significance of this independent regulation.

Our data also show that increased PDGF-A chain expression is paralleled by an elevated protein level, which was detected by immunohistochemistry as well as by Western blotting. In control animals, the staining was predominantly found in the area immediately
underlying the intima. The source of the protein is probably the media. In hypertensive animals there is an obvious increase in the staining pattern in the medial layer. Also, the staining present in the adventitia of most arteries may be attributed to the PDGF-AB isoform that is also recognized by the polyclonal antibody. Most of the staining of the adventitial layer, however, was also present in the control slides lacking the first antibody and was therefore nonspecific. Femoral arteries displayed a different staining pattern. The staining was uniformly distributed throughout the media in both controls and hypertensive rats, but more smooth muscle cells were labeled in the arteries of hypertensive animals. Again, we assume that the staining in the adventitia as well as a certain amount in the media may be attributed to the PDGF-AB isoform. However, the results obtained by the Western blot

Fig. 6. Histogram showing percentage of immunostained cells for PDGF-A in thoracic aorta and femoral arteries of 1K1C and 1K rats. Cells were counted as described in MATERIALS AND METHODS, and results are expressed as percentage (means ± SE) of stained cells out of total cell number. Only cells in intima-media were counted. *Significant difference (P < 0.05) as determined by unpaired Student's t-test.

Fig. 7. Western blots performed in nonreducing conditions showing PDGF-AA protein in extracts from aorta and femoral arteries of 1K1C and control 1K rats. The intima-media of the arteries were homogenized, and 30 µg of protein were electrophoresed in 10% polyacrylamide gels and then blotted and reacted with the antibodies. The results for the aorta and femorals are matched from the same 4 individual rats in each group. There is a single specific band at 31 kDa corresponding to the PDGF-AA homodimer and some nonspecific bands at higher molecular masses.

Fig. 8. A: differences in PDGF-AA protein in thoracic aorta and femoral arteries of 1K1C and control 1K rats. X-ray films from Western blots were subjected to densitometry, and results (means ± SE) are expressed as arbitrary units of optical density normalized to milligrams of extracted protein. *Significant difference (P < 0.05) between 1K1C and 1K rats as determined by unpaired Student's t-test. B and C: densitometric data obtained after Western blot analysis were plotted against measured wall area of thoracic and femoral arteries, respectively.
confirmed that PDGF-AA homodimer is significantly increased in both thoracic and femoral arteries of 1K1C rats. Our data show a 2.1-fold increase in the PDGF-AA homodimer protein compared with a threefold increase in PDGF-A-chain mRNA. This may be explained by the fact that a small part of the synthesized A chain is secreted as an AB and not an AA isofrom. Still, results showed a good correlation between the PDGF-AA homodimer and the wall area (Fig. 8), suggesting an important role of this particular isofrom in the hypertrophy of the wall.

In conclusion, our results indicate that 1) high blood pressure induces hypertrophy of both thoracic aorta and femoral arteries, 2) an increased expression of PDGF-A but not of PDGF-B mRNA is detected in 1K1C hypertensive animals, 3) the elevated PDGF-A mRNA level is paralleled by an increased secretion of PDGF-AA isofrom by the medial smooth muscle cells, and 4) the PDGF-A mRNA and protein levels are well correlated with both blood pressure and wall area of the arteries.

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