Role of Angiotensin Receptor Subtypes in Mesenteric Vascular Proliferation and Hypertrophy

Zemin Cao, Rachael Dean, Leonard Wu, David Casley, Mark E. Cooper

Abstract—The aim of this study was to explore the regulation of angiotensin receptors after chronic infusion with angiotensin II (Ang II) and to clarify the relative roles of the angiotensin type 1 (AT$_1$) and type 2 (AT$_2$) receptors in the mediation of Ang II–induced mesenteric vascular hypertrophy. In male Sprague-Dawley rats, Ang II infusion at a dose of 58.3 ng/min by subcutaneous osmotic minipumps for 14 days led to increased mesenteric weight and wall:lumen ratio of the vessels and proliferation of smooth muscle cells. These vascular changes were attenuated by either valsartan, an AT$_1$ receptor antagonist, at a dose of 30 mg · kg$^{-1}$ · d$^{-1}$ by gavage, or PD123319, an AT$_2$ receptor antagonist, at a dose of 830 ng/min by intraperitoneally implanted osmotic minipumps. Ang II infusion was associated with hypertension, which was prevented by valsartan, but not PD123319. $^{125}$I-Sar$^1$, Ile$^8$ Ang II binding to mesenteric vasculature was increased after Ang II infusion. Valsartan treatment was associated with reduced Ang II binding to both receptor subtypes, whereas PD123319 was associated with reduced Ang II binding to only the AT$_2$ receptor subtype. These findings suggest that the trophic and proliferative effects of Ang II on the mesenteric vasculature are mediated by both AT$_1$ and AT$_2$ receptors. (Hypertension. 1999;34:408-414.)

Key Words: angiotensin II $\cdot$ receptors, angiotensin $\cdot$ vascular proliferation $\cdot$ proliferating cell nuclear antigen

The function of angiotensin receptors in vascular proliferation and hypertrophy has been an area of ongoing debate. Contradictory functions of angiotensin type 1 (AT$_1$) and type 2 (AT$_2$) receptors have been documented by several investigators both in vivo and in vitro. Angiotensin II (Ang II) may play a dual role in cultured smooth muscle and endothelial cells, with the growth promoting effects of Ang II mediated by the AT$_1$ receptor, whereas the antiproliferative effects of Ang II occur via the AT$_2$ receptor. However, several recent studies have suggested that the AT$_2$ receptor may act in a different manner in certain contexts. For example, Ang II–induced increase in RNA synthesis in cultured A10 smooth muscle cells, a cell line without AT$_1$ receptors, could be blocked by PD123319, an AT$_2$ receptor antagonist, but not by losartan, an AT$_1$ receptor antagonist, which suggests a potential trophic action of the AT$_2$ receptor on smooth muscle cell growth. In vivo, the AT$_2$ receptor antagonist CGP 42112A, has been reported to be more effective at the prevention of neointima formation in an injured carotid artery model than the AT$_1$ receptor antagonist losartan. This finding was interpreted as an indicator that the AT$_2$ receptor plays a predominant role in neointima formation after vascular injury. However, with a transgenic technique, overexpression of the AT$_2$ receptor attenuates neointimal formation after balloon injury in the rat carotid artery.

In the rat administered Ang II chronically, the relative roles of the AT$_1$ and AT$_2$ receptor in the mediation of vascular hypertrophy have been explored by several groups. Ang II–induced aortic hypertrophy and fibrosis was prevented by the AT$_2$ receptor antagonist PD123319 but not by the AT$_1$ receptor antagonist valsartan. However, the opposite results have been reported by another group.

The difference in results between these studies is unexplained. In none of these chronic Ang II infusion studies was regulation of angiotensin receptors and in particular the AT$_2$ receptor explored. Therefore, the aim of the present study was to assess the regulation of angiotensin receptors after chronic infusion of Ang II alone or with either an AT$_1$ or AT$_2$ receptor antagonist. In addition, the effects of these angiotensin receptor antagonists on Ang II–associated mesenteric vascular proliferation and hypertrophy were directly evaluated.

Methods

Protocols

Adult male Sprague-Dawley rats (body weight 230 to 280 g) were bred and housed at the Biological Research Laboratory in the Austin and Repatriation Medical Center were used in this study. The protocols for animal experimentation and the handling of animals were in accordance with the principles established by the Animal Welfare Committee of the Austin and Repatriation Medical Center.

In protocol 1, 40 rats were randomly allocated into 4 groups (n=10/group) and treated for 14 days. Group 1 received a vehicle...
infusion of 0.15 mol/L sodium chloride and 1 mmol/L acetic acid via Alzet osmotic minipumps (Model 2002, Alzet Corp) implanted subcutaneously in the midscapular region. Animals were anesthetized with enflurane (Ethrane). Group 2 was infused with human Ang II (Auspex) at a concentration of 7 mg/mL. On the basis of the pump rate of the minipumps (0.5 μL/h), Ang II was administered at a dose of 58.3 ng/min, a dose shown to induce hypertension and vascular hypertrophy.15 Group 3 received the Ang II infusion plus the AT2 receptor antagonist valsartan (provided by Dr Marc de Gasparo, Novartis, Basel, Switzerland) at a dose of 30 mg·kg−1·d−1 by daily gavage; this dose reduces blood pressure in Sprague-Dawley rats.12,13 Group 4 was infused with Ang II subcutaneously and the AT1 receptor antagonist PD123319 (provided by Dr Joan Keiser, Parke-Davis, Ann Arbor, Mich) via an intraperitoneally implanted Alzet minipump (Model 2002). PD123319 was dissolved at a concentration of 100 mg/mL with sterile water. On the basis of the pump rate of the minipumps (0.5 μL/h), PD123319 was administered at 830 ng/min. This dose is in the range used by other groups14 and is the maximal dose that could be achieved with this model of minipump in our laboratory.

In protocol 2, the effect of treatment with valsartan (n=6) or PD123319 (n=7) alone on mesenteric vasculature was evaluated in Sprague-Dawley rats. Valsartan and PD123319 were administered as in protocol 1. To explore the possible influence of intraperitoneal implantation of minipumps on mesenteric vasculature, an additional group was implanted intraperitoneally with minipumps that contained vehicle alone (n=7).

Systolic blood pressure (SBP) was measured by indirect tail-cuff plethysmography in prewarmed, unanesthetized animals as previously described.15 The animals were killed at day 14. Blood samples were collected from the tail vein of conscious rats before the animals were killed for the measurement of plasma renin activity (PRA).16 Animals were anesthetized by intravenous injection of pentobarbitone sodium at a dose of 60 mg/kg body wt (Boehringer Ingelheim). The mesenteric arteries (n=7/group, protocol 1) were perfused in vivo at arterial pressure via an intra-aortic cannula. The vessels were first flushed of blood with saline and then fixed with 2.5% glutaraldehyde.17 The mesenteric vessels were removed and stripped of surrounding fat, connective tissue, and veins.17 The vessels were weighed, fixed in 10% formalin, and paraffin-embedded by use of the standard procedures.

 Autoradiography

Mesenteric arteries (n=3/group, protocol 1) were dissected and placed into ice-cold saline and stripped of surrounding fat, connective tissue, and veins. Tissue was then snap-frozen in liquid nitrogen and stored at −80°C. Sections (20 μm thick) were cut on a cryostat at −20°C, dehydrated overnight under reduced pressure at 4°C, and then stored at −80°C in sealed containers with silica gel. Autoradiographic localization of Ang II receptors was performed as described previously.18 Briefly, Ang II receptor binding sites were labeled with the analogue of Ang II, 125I-Sar(1), Ile(8) Ang II. The slide-mounted sections were preincubated for 15 minutes in 10 mmol/L sodium phosphate buffer (pH 7.4) followed by 1 hour of incubation in a fresh volume of the same buffer that contained 0.2 μCi/mL (~90 pmol) 125I-Sar(1), Ile(8) Ang II, 0.2% BSA, and 0.3 mmol/L bacitracin. AT1 receptor binding was determined by the binding that remained in the presence of the AT1 receptor antagonist PD123319 (10−3 mol/L). AT2 receptor binding was determined by the binding that remained in the presence of the AT2 receptor antagonist Dup 753 (10−5 mol/L). Nonspecific binding was determined in parallel incubations in the presence of 10−5 mol/L PD123319 and 10−7 mol/L Dup 753. After the sections were incubated, they were washed 4 times for 1 minute each in ice-cold buffer, dried under a stream of cold air, and exposed to Agfa Scopix CR3B x-ray film at room temperature for 2 weeks. A set of radioactivity standards was included in each cassette.

After the films were exposed, they were processed and the optical densities quantified by a microcomputer imaging device (MCID Imaging system) coupled to an IBM-AT computer. A calibration curve of optical density versus radioactivity density was constructed by the computer program with the radioactivity standards. This enabled conversion of the data into dpm/mm2.18 Binding densities were calculated as the difference between the total binding and nonspecific binding, respectively. The slides were then coated in photographic emulsion (Ilford K5) and stored for 4 weeks. Slides were developed in phenisol developer (Ilford K5), fixed, and stained with hematxylon-cosin for light microscopy.

 Immunohistochemistry

Four-micron paraffin sections of mesenteric artery were cut, dehydrated, and used for immunohistochemistry. Endogenous peroxidase was inactivated with 3% hydrogen peroxide (H2O2) in methanol for 20 minutes, then blocked with a protein block agent for 20 minutes. The sections of vessels were labeled with either a mouse anti-human α-smooth muscle actin antibody or cell nuclear antigen proliferating (PCNA, DAKO A/S). The multi-link swine anti-goat-, mouse-, and rabbit immunoglobulin (DAKO A/S) was used as the secondary antibody; this was then followed by peroxidase-conjugated streptavidin. Detection was accomplished by reaction with 3,3′-diaminobenzidine tetrahydrochloride (Sigma Chemical Co).

 Histomorphometry

Mesenteric vascular structure was assessed by quantitative histomorphometry as previously described.13,17 A video imaging system (Visioscan Pro 32) and an associated online microscope and computer were used to count the number of PCNA positive cells in a manner similar to that described by Kato et al.19 In brief, the cells that contained PCNA were counted manually in the mesenteric media and adventitia. The areas of the media and adventitia were also measured. PCNA positive cells were expressed as the cell number per μm2. In the adventitia, only those positively stained cells located within 40 μm of the external elastic lamina were included.

 Statistical Analysis

Data were analyzed by ANOVA by use of Statview SE (Brainpower) on a Macintosh Computer. Comparisons of group means were performed by Fisher’s least significant difference method. Because PRA did not have a normal distribution, this parameter was analyzed after logarithmic transformation. Data are shown as mean±SEM. P<0.05 was considered statistically significant.

 Results

 Protocol 1

Ang II–infused rats gained less weight than vehicle-treated animals. This influence of Ang II on body weight was prevented by co-administration of Ang II with valsartan, but not with PD123319 (Table 1). Ang II infusion was associated with hypertension during the experimental period, which was prevented by concomitant treatment with valsartan but not PD123319 (Table 1). Ang II infusion was associated with markedly reduced PRA levels. Valsartan treatment increased PRA levels to more than those observed with vehicle alone. Administration of PD123319 did not influence the effect of Ang II on PRA (Table 1).

 Mesenteric Vessel Structure

Mesenteric vessel weight and the mesenteric vessel weight to body weight ratio were increased 2-fold in Ang II infused animals. This influence of Ang II on body weight was prevented by co-administration of Ang II with valsartan, but not with PD123319 (Table 1). Ang II infusion was associated with hypertension during the experimental period, which was prevented by concomitant treatment with valsartan but not PD123319 (Table 1). Ang II infusion was associated with markedly reduced PRA levels. Valsartan treatment increased PRA levels to more than those observed with vehicle alone. Administration of PD123319 did not influence the effect of Ang II on PRA (Table 1).
of Ang II–induced increases in mesenteric vascular weight or wall:lumen ratios (Figure 1, top).

### Proliferative Cell Nuclear Antigen

Ang II infusion resulted in increased PCNA staining in the mesenteric vasculature, which was assessed by a 5-fold increase in PCNA positive cells in the medial layer and a 2-fold increase in PCNA positive cells in the adventitial layer compared with vehicle-infused rats. Treatment of Ang II–infused rats with either valsartan or PD123319 was associated with a decrease in PCNA positive cells to vehicle-infused levels in both media and adventitia (Figure 1, middle and bottom; Figure 2).

### In Vitro Autoradiography of Angiotensin Receptors

In vehicle-infused rats, both AT1 and AT2 receptors were present in mesenteric vessels. AT1 receptors were the predominant subtype (88%). The density of Ang II binding sites was increased after Ang II infusion, with a 70% increase in AT1 and a 4-fold increase in AT2 receptor subtypes. Treatment with valsartan was associated with a reduction in both AT1 and AT2 receptor binding. Administration of PD123319 was associated with a decrease in the AT2 receptor, but not the AT1 receptor subtype (Table 2, Figure 3). Binding sites for both AT1 and AT2 receptors were in the medial and adventitial layers (Figure 4A and 4B). The same distribution of AT1 and AT2 receptors was observed after Ang II infusion (Figure 4C and 4D).

### Protocol 2

Weight gain was similar among the various treatment groups, and there was no significant difference when compared with control animals (Table 3). Valsartan resulted in a decrease in SBP and an increase in PRA over the experimental period. PD123319 or implantation of the minipump intraperitoneally did not significantly influence blood pressure or PRA (Table 3).

No significant difference existed in mesenteric vessel weight or the ratio of mesenteric vessel weight to body weight between the valsartan treated and control rats. Intraperitoneal administration of PD123319 or vehicle alone via the osmotic minipumps was associated with an increase in vessel weight and in the ratio of mesenteric vessel weight to body weight (Table 3). However, the wall:lumen ratio of mesenteric arteries was not affected by any of the treatments compared with control animals. There was no significant difference in the number of PCNA positive cells in the medial or adventitial layers among the various treatment groups (Table 3).

### Discussion

The present study has confirmed and extended previous findings that Ang II infusion promotes the growth of smooth muscle cells and induces vascular hypertrophy in rats. Administration of both the AT1 and AT2 receptor antagonists was associated with attenuation of mesenteric vascular hypertrophy and smooth muscle cell proliferation. These results

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**TABLE 1. Effects of Treatment on Body Weight, SBP, PRA, and Mesenteric Vessel Weight in Protocol 1**

<table>
<thead>
<tr>
<th></th>
<th>BW, g</th>
<th>SBP mm Hg</th>
<th>PRA, nmol·L⁻¹·h⁻¹</th>
<th>Mes. W, mg</th>
<th>Mes. W/BW, mg/g</th>
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<tr>
<td>Vehicle</td>
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<td>Ang II</td>
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<td>220±12*</td>
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<td>Ang II + Valsartan</td>
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<td>247±10</td>
<td>321±11†</td>
<td>127±5†</td>
<td>143±5†</td>
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<tr>
<td>Ang II + PD123319</td>
<td>7</td>
<td>264±4</td>
<td>259±12*</td>
<td>185±7*</td>
<td>210±11*</td>
</tr>
</tbody>
</table>

BW indicates body weight; Mes. W, mesenteric vascular weight; PRA, plasma renin activity; Ang II, angiotensin II. *P<0.01 vs Vehicle; †P<0.05, ‡P<0.01 vs Ang II.
are consistent with findings obtained from cultured rat cardiac fibroblasts, in which Ang II–stimulated collagen synthesis was mediated by both AT1 and AT2 receptors.20 In cultured quiescent vascular smooth muscle cells, Ang II elevates the nuclear transcription factor–κB (NF-κB), which is thought to participate in the regulation of cell proliferation and vascular damage.21 This occurs via stimulation of both AT1 and AT2 receptors.21 In aortic smooth muscle cells, Ang II–induced changes in nuclear calcium levels are mediated by both AT1 and AT2 receptors.22 This increase in nuclear calcium is thought to play a pivotal role in the mediation of the trophic response to Ang II.22 Furthermore, in cultured mouse spleen lymphocytes, the stimulatory effect of Ang II on proliferation has been shown to be mediated by both angiotensin receptor subtypes.23

In protocol 2, intraperitoneal implantation of osmotic minipumps that delivered either PD123319 or vehicle was associated with increased mesenteric vessel weight. This may be due to a nonspecific reaction to the minipumps or to the fluid delivered from the minipumps into the abdominal cavity. However, treatment with either valsartan or PD123319 in normotensive rats did not influence vascular structure. Consistent with these in vivo findings are in vitro studies that indicate that AT1 and AT2 receptor antagonists inhibit the activation of NF-κB in Ang II–stimulated smooth muscle cells in culture but not in quiescent cells.21 This study suggests that blood pressure and PRA respond differently to the AT1 and AT2 antagonists in both Ang II–induced hypertension and in the normotensive physiological state. Furthermore, these findings confirm that the effects of Ang II on regulation of blood pressure and PRA are mediated by the AT1 receptor and not the AT2 receptor. Other studies have shown that the administration of PD123319 in the rat, even at a very high dose, has no effects on blood pressure, plasma Ang II levels, or cardiovascular hemodynamics.9,24,25 These findings have been interpreted as indicating that PD123319 does not act on the AT1 receptor. However, it has been suggested that high doses of PD123319 may act as an AT1 antagonist.26 In the present study, it is unlikely that PD 123319 acted as an AT1 receptor antagonist because in vitro autoradiographic assessment of Ang II binding suggested that PD123319 inhibited the AT2 receptor but did not act as an AT1 receptor antagonist on the mesenteric vasculature. Indeed, Macari et al14 have suggested that the concentration of PD123319 required to exert an effect on the AT1 receptor is >100 μmol/L, a concentration that is unlikely to have been achieved in the present study. The lack of effect on the AT1 receptor with doses similar to those used in the present study has been previously reported.9 Nevertheless, in view of the difference in the mode of administration of
Ang II can also induce vascular hypertrophy without significantly raising blood pressure.\textsuperscript{11,27} The cause for this vascular hypertrophy, independent of systemic hypertension, remains unclear. The possibility that this involves activation of the AT\textsubscript{2} receptor, with subsequent proliferative effects without influencing blood pressure, remains to be determined. Recently, Otsuka et al\textsuperscript{28} reported a significantly enhanced mRNA expression for the AT\textsubscript{2} receptors in the aorta of spontaneously hypertensive rats (SHR). Treatment with the AT\textsubscript{2} receptor antagonist PD123319 was associated not only with a decrease in mRNA expression for the AT\textsubscript{2} receptor but also with a reduction in the medial cross-sectional area of the aorta.\textsuperscript{28} This provides evidence for a role for the AT\textsubscript{2} receptor in the process of smooth muscle hypertrophy in the aorta from SHR.\textsuperscript{28} This reduction in vascular hypertrophy with an AT\textsubscript{2} receptor antagonist is consistent with previous studies that used either the model of Ang II infusion\textsuperscript{9} or carotid artery injury.\textsuperscript{7}

The regulation of angiotensin receptors and the relative balance of AT\textsubscript{1} and AT\textsubscript{2} receptors in the setting of elevated plasma Ang II levels has not been fully explored. With the use of radioligand binding studies, it has been shown that there is a similar distribution of AT\textsubscript{1} and AT\textsubscript{2} receptor subtypes in the vascular system, albeit in the normal physiological context.\textsuperscript{29} However, it has been suggested that after Ang II infusion, there is increased expression of the AT\textsubscript{2} rather than the AT\textsubscript{1} receptor in hypertrophied rat hearts.\textsuperscript{29,30} With the use of radioligand binding techniques, we have shown for the first time that both AT\textsubscript{1} and AT\textsubscript{2} binding sites are present in the mesenteric vasculature from the rat with the AT\textsubscript{1} receptor being the predominant subtype. Upregulation of both AT\textsubscript{1} and AT\textsubscript{2} receptor subtypes in mesenteric vasculature was observed after Ang II infusion. This increase in receptor number is particularly

**Figure 3.** Representative macroscopic autoradiographs of total Ang II, AT\textsubscript{1}, and AT\textsubscript{2} binding density in protocol 1. A, vehicle infusion; B, Ang II infusion; C, Ang II infusion plus valsartan; and D, Ang II infusion plus PD123319. Column 1 indicates total Ang II binding; 2, AT\textsubscript{1} binding; 3, AT\textsubscript{2} binding; and 4, nonspecific binding.

**Figure 4.** Light microscopic autoradiographs show AT\textsubscript{1} and AT\textsubscript{2} binding sites in the smooth muscle cell and in the adventitia in rats infused with vehicle (A, AT\textsubscript{1}; and B, AT\textsubscript{2}) or Ang II (C, AT\textsubscript{1}; and D, AT\textsubscript{2}). Labeling is represented by silver grains (black dots) that overlie cells. Sections are stained with hematoxylin and eosin. Magnification ×400.
evident with respect to the AT2 receptor subtype with a 4-fold increase after Ang II infusion. Upregulation of the AT2 receptor has been described in other pathological states including hypertension, diabetes, myocardial infarction, and ischemia. Recently, it has been shown that angiotensin II promotes expression of the AT1 receptor in the kidney. These findings are consistent with the present study that noted a increase in the AT1 receptor binding with angiotensin II infusion.

The reduction in AT1 receptor binding with valsartan and the decrease in AT2 receptor binding with PD123319 is consistent with the known effects of these antagonists on angiotensin receptors. However, valsartan treatment was also associated with a reduction in AT2 binding density. The reason for this reduction in AT2 receptor density by treatment with valsartan is unknown. Because valsartan therapy was associated with reduced vascular injury and vascular injury is associated with increased AT2 receptor density, it is possible that the decrease in AT2 receptor binding with valsartan occurred as a consequence of valsartan’s action as a vasoprotective agent. It is unlikely that this effect of valsartan is at the level of AT2 receptor gene expression because it has been shown in the SHR that losartan does not affect vascular AT2 receptor gene expression. Because administration of either valsartan or PD123319 is associated with attenuation of vascular proliferation and hypertrophy, it is likely that both receptor subtypes are involved in the mediation of angiotensin II–induced vascular injury.

**Acknowledgments**

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**References**


**TABLE 3. Effects of Treatment on Body Weight, SBP, PRA, Mesenteric Vessel Weight, and PCNA in Protocol 2**

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Data were shown as mean±SEM. BW, body weight; Mes. W, mesenteric vascular weight; W/L, wall:lumen; PCNA, proliferating cell nuclear antigen.

*P<0.05 vs Control, †P<0.01.


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