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Circulation. 2002;105:2296-2302; originally published online April 29, 2002;
doi: 10.1161/01.CIR.0000016049.86468.23
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Structure, Endothelial Function, Cell Growth, and Inflammation in Blood Vessels of Angiotensin II–Infused Rats

Role of Peroxisome Proliferator–Activated Receptor-γ

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Background—Pioglitazone and rosiglitazone, thiazolidinedione peroxisome proliferator–activated receptor-γ (PPARγ) activators, reduce blood pressure (BP) in some hypertensive models by unclear mechanisms. We tested the hypothesis that pioglitazone or rosiglitazone would prevent BP elevation and vascular dysfunction in angiotensin (Ang) II–infused rats by direct vascular effects.

Methods and Results—Sprague-Dawley rats received Ang II (120 ng · kg^{-1} · min^{-1} SC) with or without pioglitazone (10 mg · kg^{-1} · d^{-1}) or rosiglitazone (5 mg · kg^{-1} · d^{-1}) for 7 days. Systolic BP, elevated in Ang II–infused rats (176±5 mm Hg) versus controls (109±2 mm Hg, $P<0.01$), was reduced by pioglitazone (134±2 mm Hg) or rosiglitazone (123±2 mm Hg). In mesenteric small arteries studied in a pressurized myograph, media/lumen ratio was increased ($P<0.05$) and acetylcholine-induced relaxation impaired in Ang II–infused rats ($P<0.05$); both were normalized by the thiazolidinediones. In Ang II–infused rats, vascular DNA synthesis (by ^{3}H-thymidine incorporation); expression of cell cycle proteins cyclin D1 and cdk4, angiotensin II type 1 receptors, vascular cell adhesion molecule-1, and platelet and endothelial cell adhesion molecule; and nuclear factor-κB activity were increased. These changes were abrogated by pioglitazone or rosiglitazone.

Conclusions—Thiazolidinedione PPAR-γ activators attenuated the development of hypertension, corrected structural abnormalities, normalized cell growth, and improved endothelial dysfunction induced by Ang II and prevented upregulation of angiotensin II type 1 receptors, cell cycle proteins, and proinflammatory mediators. Thiazolidinediones may be useful in the prevention and/or treatment of hypertension, particularly when it is associated with insulin resistance or diabetes mellitus. **(*Circulation*. 2002;105:2296-2302.)**

Key Words: hypertension ■ arteries ■ remodeling ■ muscle, smooth ■ inflammation

Insulin resistance has emerged as a mechanism linking diabetes mellitus and hypertension.[1] Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone are high-affinity ligands for peroxisome proliferator–activated receptor (PPAR)-γ, a transcription factor of the nuclear hormone receptor superfamily,[2] and are used as insulin-sensitizing drugs in type II diabetes mellitus. TZDs increase transcription of certain insulin-sensitive genes by binding to nuclear PPAR-γ, which together with the retinoid X receptor binds to specific DNA sequences, the peroxisome proliferator response elements.[3] Expression of PPAR-γ, initially thought to be restricted to adipose tissue, is now known to occur in endothelium,[4] vascular smooth muscle cells (VSMCs),[5] and monocytes/macrophages.[6]

Angiotensin (Ang) II plays a major role in hypertension. Ang II–induced hypertensive rats exhibit abnormal vascular structure.[7] VSMC growth, apoptosis, cell migration, inflammation, and increased deposition of extracellular matrix proteins such as collagen and fibronectin, as well as changes in anchoring of cells to the fibrillar components of the extracellular matrix, are some of the processes that contribute to vascular remodeling induced by Ang II.[8]

TZDs have blood pressure (BP)–lowering effects,[9,10] but mechanisms for this are unclear. PPAR-γ agonists may directly modulate vascular structure and function independently of their role on lipid metabolism. Here, we tested the hypothesis that PPAR-γ activators such as pioglitazone or rosiglitazone have effects on Ang II type 1 (AT_1) receptors and that Ang II–induced increases in DNA synthesis, cell cycle proteins, nuclear factor-κB (NF-κB), vascular cell adhesion molecule-1 (VCAM-1), and platelet and endothelial cell adhesion molecule (PECAM) are abrogated by these agents in Ang II–infused rats.

Received December 28, 2001; revision received February 21, 2002; accepted February 21, 2002.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000016049.86468.23**

TABLE 1. Body Weight, Systolic BP, Plasma Renin Activity, Aldosterone, Cholesterol, Triacylglycerol, and Nonesterified Fatty Acids in Ang II–Infused Rats±PPAR-γ Activators After 7-Day Treatment

Parameter	Control	Ang II	Ang+ Pioglitazone	Ang+ Rosiglitazone	Pioglitazone	Rosiglitazone
Body weight, g	241±5	251±4	245±4	244±4	239±5	246±3
Systolic BP, mm Hg	109±2	176±5†	134±2†‡	123±2*‡	119±3‡	129±2†‡
Plasma renin activity, ng angiotensin I/mL per hour	2.97±0.52‡	0.56±0.36†	0.19±0.1†	0.30±0.30†	3.19±0.55‡	2.56±0.36‡
Aldosterone, pg/mL	169±28	290±104*	368±129*	164±48	110±14	52±11*
Cholesterol, mmol/L	1.16±0.11	1.50±0.12	1.72±0.06	1.66±0.06	1.62±0.15	1.57±0.11
Triacylglycerol, mmol/L	0.89±0.12	0.84±0.12	1.01±0.11	0.61±0.03	0.77±0.05	0.74±0.03
Nonesterified fatty acids, mEq/L	0.26±0.04	0.23±0.03	0.31±0.06	0.2±0.03	0.28±0.04	0.26±0.04

Data are mean±SEM of 6 to 8 rats.
*$P<0.05$, †$P<0.01$ vs control; ‡$P<0.05$ vs Ang II group.

Methods

Animal Experiments

The study was approved by the Animal Care Committee of the Clinical Research Institute of Montreal and followed guidelines of the Canadian Council for Animal Care. Male Sprague-Dawley rats (weight 200 g; Corporation Charles River Canada, Saint-Constant, Quebec, Canada) were infused subcutaneously by use of Alzet osmotic minipumps (Alza Corp) with Ile^5-Ang II (Peninsula) at a dose of 120 ng · kg^{-1} · min^{-1} for 7 days. Pioglitazone (10 mg · kg^{-1} · d^{-1}) and rosiglitazone (5 mg · kg^{-1} · d^{-1}) were offered mixed with food. Ang II–infused rats were also treated with hydralazine (25 mg · kg^{-1} · d^{-1}) in drinking water to evaluate effects of BP lowering. Systolic BP was measured by the tail-cuff method. Rats were not fasted overnight, and they were killed by decapitation. The mesenteric bed was dissected; one segment was used for preparation of small arteries, and the rest was cleaned of fat, frozen in liquid nitrogen, and kept at −80°C for Western blot assay and for DNA extraction. A portion of aorta was fixed in 10% buffered formalin solution and embedded in paraffin. Tissue sections (7 μm thick) were prepared for immunohistochemical analysis. Fat and endothelium were removed from another portion of aorta that was then frozen in liquid nitrogen and kept at −80°C for measurement of NF-κB activity.

Preparation and Study of Small Arteries

Third-order superior mesenteric arteries (length ≈2 mm) were placed in cold physiological salt solution containing (in mmol/L) NaCl 120, $NaHCO_3$ 25, KCl 4.7, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 2.5, EDTA 0.026, and glucose 5.5. They were mounted on glass microcannulas in a pressurized myograph.[11] Endothelium-dependent relaxation was assessed with cumulative doses of acetylcholine (10^{-9} to 10^{-4} mol/L) after precontraction with 10^{-5} mol/L norepinephrine. Endothelium-independent relaxation was assessed with cumulative doses of sodium nitroprusside (SNP; 10^{-8} to 10^{-3} mol/L). Vessels were then deactivated by perfusion with Ca^{2+}-free physiological salt solution containing 10 mmol/L EGTA for 30 minutes. Lumen and media were measured with intraluminal pressure at 45 mm Hg.

Evaluation of Collagen Deposition in Aorta

Paraffin-embedded sections of aorta were stained with Sirius Red. Collagen in the media was quantified microscopically with the Northern Eclipse imaging program.

Evaluation of DNA Synthesis

DNA synthesis in mesenteric arteries was evaluated by radiolabeled ^{3}H-thymidine incorporation.[12] Rats received intraperitoneal injections of [methyl-^{3}H] thymidine (0.5 mCi/kg, ICN Biomedicals Inc) 24 hours before they were killed. DNA was extracted with phenol/chloroform and its concentration determined spectrophotometrically. DNA specific activity (cpm/100 μg of DNA) reflecting the incorporation of ^{3}H-thymidine into smooth muscle DNA over the last 24 hours in vivo was measured by scintillation counting.

Western Blot Analysis of Cyclin D1, cdk4, VCAM-1, PECAM, PPAR-γ, and AT_1 and AT_2 Receptors

Protein was extracted from frozen tissue,[12] and concentration was determined with the Micro BCA protein assay kit (Pierce). Aliquots were separated by electrophoresis on a 10% to 15% polyacrylamide gel at 100 V for 1 hour and transferred onto a polyvinylidene difluoride membrane in a cooling system at 100 V for 1 hour. Membranes were incubated with specific antibody to cyclin D1, cdk4, VCAM-1, PECAM, PPAR-γ, and AT_1 and AT_2 receptors (Santa Cruz Biotechnology Inc). Signals were revealed with chemiluminescence and visualized autoradiographically. Optical density of bands was quantified by scanning and with ImageQuant (Molecular Dynamics). The density of the bands from each blot was normalized to that of controls (taken as 100%). Mean±SEM values were calculated from 4 blots.

Electrophoretic Mobility Shift Assay for NF-κB

Frozen aorta was homogenized; suspended in solution containing 50 mmol/L Tris (pH 7.4), 1 mmol/L sodium orthovanadate, 1 μg/mL pepstatin, 1 μg/mL aprotinin, and 1 μg/mL leupeptin; and centrifuged (4000*g*, 4 minutes, 4°C).[13] The resuspended pellet was lysed for 30 minutes in 20 mmol/L HEPES, pH 7.9, containing 350 mmol/L NaCl, 20% glycerol, 1 mmol/L $MgCl_2$, 0.5 mmol/L EDTA, 0.1 mmol/L EGTA, 1% NP-40, 1 mmol/L PMSF, 1 mmol/L sodium orthovanadate, 1 μg/mL pepstatin, 1 μg/mL aprotinin, and 1 μg/mL leupeptin and centrifuged (13 000*g*, 10 minutes, 4°C). The supernatant was stored at −80°C. Protein concentration was quantified by BioRad reagent. Twenty micrograms of nuclear protein was incubated at room temperature for 30 minutes in binding reaction medium (50 mmol/L Tris-HCl, 250 mmol/L NaCl, 20% glycerol, 2.5 mmol/L EDTA, 2.5 mmol/L DTT, 5 mmol/L $MgCl_2$, and 0.25 mg/mL poly dI-dC) with 0.5 ng of ^{32}P-dATP end-labeled double-stranded oligonucleotide containing the NF-κB binding site (Promega, 5′-AGTTGAGGGGACTTTCCCAGGC-3′, based on the rat sequence) from the major histocompatibility complex enhancer. HeLa cell nuclear extracts and water were respectively positive and negative controls. NF-κB (p65-x) antibody from Santa Cruz was used for supershift. In competition assays, 50 ng of unlabeled oligonucleotides was used. The DNA-protein complexes were analyzed on 4% polyacrylamide gel in 0.5X Tris-borate-EDTA buffer. The gel was then dried and exposed to ^{32}P-sensitive screen. Optical density in the region of NF-κB (p65) was quantified for each lane with the PhosphoImager system. Mean±SEM values were calculated from 3 electrophoretic mobility shift assays.

Measurement of Plasma Renin Activity, Aldosterone, and Lipids

Plasma renin activity was measured by radioimmunoassay of Ang I produced after a 2-hour incubation of plasma at 37°C and pH 6.5.[14]

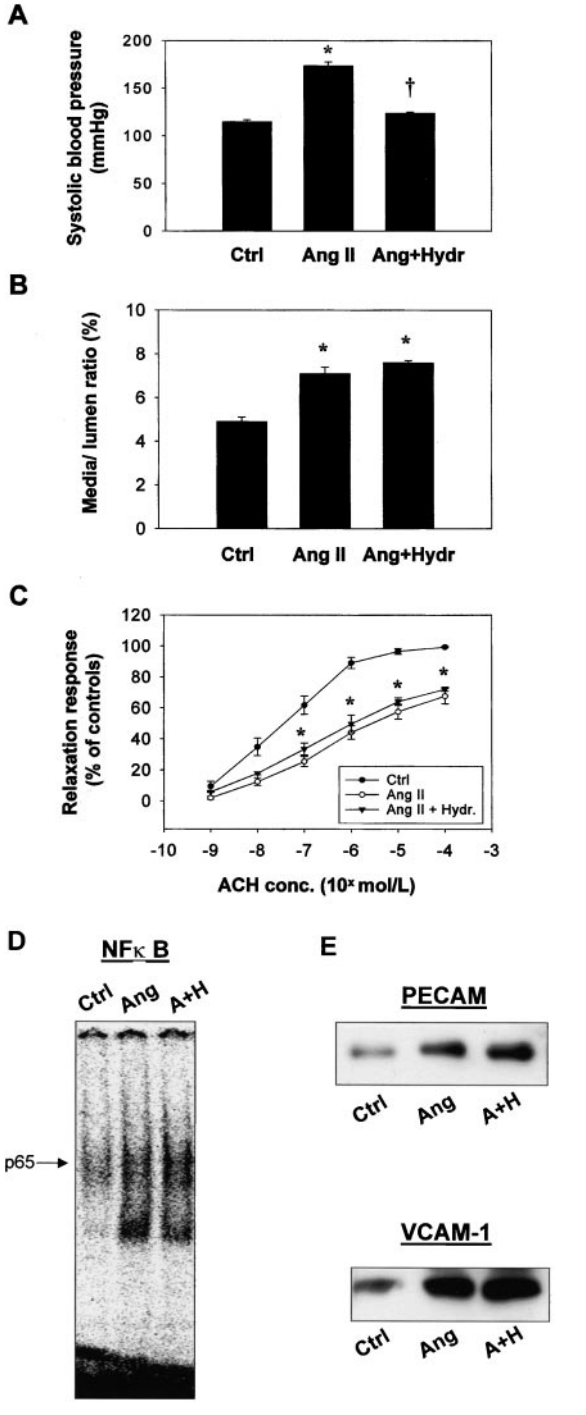


Figure 1. A, Systolic BP in Ang II–infused rats treated without or with hydralazine (Hydr) for 7 days. Results are mean±SEM (n=5 to 8 per group). *$P<0.05$ vs control, †$P<0.05$ vs Ang II group. B, Media/lumen ratio (as %) in small mesenteric arteries of Ang II–infused rats treated without or with hydralazine for 7 days. Results are mean±SEM (n=5 to 8 per group). *$P<0.05$ vs control. C, Endothelium-dependent relaxation in response to acetylcholine (ACH) in small mesenteric arteries of Ang II–infused rats treated without or with hydralazine for 7 days. Results are mean±SEM (n=5 to 8 per group). Relaxation is expressed as percent increase in intraluminal diameter after precontraction with 10^{-5} mol/L norepinephrine. *$P<0.05$ vs control. D, Electrophoretic mobility shift assay of NF-κB activity in aorta, representative of results of 4 experiments. E, Representative Western blot of PECAM (top) and VCAM-1 (bottom) in blood vessel. Data shown are representative of results of 4 experiments. Ctrl indicates control; conc., concentration; and A+H, Ang II infusion plus hydralazine.

Plasma aldosterone was measured with the ALDOCTK-2 (P2714) assay kit from DiaSorin. Plasma was assayed for total (free and esterified) cholesterol and triacylglycerol with a COBAS MIRA-S automated analyzer with enzymatic reagents (Hoffman-LaRoche). Nonesterified fatty acids were measured by enzymatic colorimetric method (Wako NEFA C test kit).

Data Analysis

Values are presented as mean±SEM. Results were compared by 1-way ANOVA, followed by Tukey-Kramer test. $P<0.05$ was considered significant.

Results

Body Weight, BP, Plasma Renin Activity, Aldosterone, and Lipids

After 7-day treatment, body weight was similar in all groups (Table 1). The BP increase induced by Ang II infusion ($P<0.01$ versus control) was abolished by pioglitazone and rosiglitazone (Table 1) and, in parallel experiments, by hydralazine (124±1 mm Hg; Figure 1A). Rosiglitazone slightly increased BP in normal rats.

As expected, plasma renin activity was significantly depressed in Ang II–infused rats and was unaffected by pioglitazone or rosiglitazone (Table 1). The plasma aldosterone/renin activity ratio rose 100-fold with Ang II and was unaffected by pioglitazone or rosiglitazone. Ang II, pioglitazone, and rosiglitazone had no effect on plasma cholesterol, triacylglycerol, or nonesterified fatty acids.

Collagen Deposition in Aorta

Ang II, pioglitazone, and rosiglitazone did not affect vascular collagen deposition after the 7-day Ang II infusion (Table 2).

Morphology and Endothelial Function of Resistance Arteries

Ang II infusion resulted in an increase ($P<0.05$) in media/lumen ratio of resistance arteries (Table 2), which was normalized by treatment with pioglitazone or rosiglitazone (Table 2). Hydralazine did not affect vascular structural changes induced by Ang II (Figure 1B). Media cross-sectional area of resistance arteries was similar in all groups.

Ang II–infused rats exhibited impaired acetylcholine-induced relaxation (Figures 1C and 2A), which improved ($P<0.05$) under pioglitazone and rosiglitazone (Figure 2A) but not hydralazine (Figure 1C). Endothelium-independent relaxation by SNP was similar in all groups (Figure 1B). Relaxation to acetylcholine and SNP was unaffected by the TZDs alone (data not shown).

Resistance Artery DNA Synthesis and Expression of Cell Cycle Proteins

Vascular DNA synthesis (^{3}H-thymidine incorporation) increased 1.8-fold in Ang II–infused rats (Figure 3A) and decreased with pioglitazone and rosiglitazone. Expression of cyclin D1 and cdk4 increased 3- and 4-fold, respectively, in Ang II–infused rats (Figure 3B). This effect was abrogated by the TZDs (Figure 3B).

Vascular Expression of Angiotensin Receptors

Expression of AT_1 and AT_2 receptors in resistance arteries of Ang II–infused rats increased 2-fold (Figure 4). Pioglitazone- and rosiglitazone-treated Ang II–infused rats had normal levels of AT_1

TABLE 2. Collagen Deposition in Aorta and Morphological Characteristics of Pressurized Resistance Arteries From Ang II–Infused Rats±PPAR-γ Activators After 7-Day Treatment

Parameter	Control	Ang II	Ang+ Pioglitazone	Ang+ Rosiglitazone	Pioglitazone	Rosiglitazone
Aorta						
Collagen volume density, %	32.0±1.2	30±0.9	29.0±1.2	29.0±1.5	31.0±1.4	32.0±1.4
Resistance arteries						
Lumen diameter, μm	238±12	201±11	270±22	257±22	273±20	220±13
Media thickness, μm	20.9±0.9	25.7±2.0	21.7±1.1	21.0±1.2	21±0.7	20.6±0.6
Media/lumen ratio, %	8.8±0.2	13.0±1.6*	8.3±0.9†	8.3±0.6†	7.7±0.8†	9.4±0.3†
Media cross-sectional area, $10^3 \times \mu m^2$	18.3±0.9	18.1±1.6	19.7±0.9	18.6±2.5	18.9±1.1	15.6±1.3

Data are mean±SEM of 6 to 8 rats.
*$P<0.05$ vs control; †$P<0.05$ vs Ang II group.

receptors. Expression of AT_2 receptors increased 2-fold in rats treated with the TZDs, whether Ang II–infused or not.

Vascular Expression of NF-κB and Adhesion Molecules

NF-κB, which regulates expression of inflammatory mediators, was activated 3-fold in blood vessels of Ang II–infused rats (Figures 5A and 1D), and VCAM-1 and PECAM expression increased significantly (Figures 5B and 5C and Figure 1E). These effects were abolished by pioglitazone and rosiglitazone (Figures 5B and 5C) but not by hydralazine (Figures 1D and 1E). The TZDs alone had no effect on NF-κB, VCAM-1, or PECAM.

Vascular Expression of PPAR-γ

PPAR-γ expression in mesenteric arteries was unaffected by Ang II but was enhanced by pioglitazone or rosiglitazone (Figure 6).

Discussion

In this study, pioglitazone and rosiglitazone prevented hypertension in Ang II–infused rats and abrogated the structural, functional, and molecular changes in blood vessels. We show the novel finding that the PPAR-γ activators had direct effects on the vascular wall, with downregulation of AT_1 receptors and upregulation of AT_2 receptors that led to inhibition of cell growth and inflammation.

TZDs have antihypertensive effects in other hypertensive models.[9,10] The novel finding that these agents reduced resistance artery remodeling may be explained by a direct action of TZDs on the vessel wall. BP lowering does not appear to play a role, because hydralazine decreased BP without any effect on vascular structure, endothelial function, or inflammatory mediators. These in vivo data confirm and extend results from in vitro studies in which PPAR-γ ligands were shown to downregulate AT_1 receptor expression[15–17] and inhibit Ang II–stimulated DNA synthesis in VSMCs[18] by modulation of cyclin-dependent kinase inhibitors.[19] Pioglitazone and rosiglitazone also decreased cell growth in small arteries. We recently found that rosiglitazone induced VSMC apoptosis, which could contribute to this effect (unpublished data). Although molecular mechanisms remain to be clarified, inhibition of growth and acceleration of apoptotic rate by PPAR-γ via increased expression of AT_2 receptors may decrease the cell proliferation induced by Ang II via AT_1 receptors. Ang II also induces vascular remodeling via collagen deposition.[8,20] The absence of changes in collagen found during the short 7-day Ang II infusion in the present study may contribute to the absence of net vascular growth observed in the Ang II–infused groups. Indeed, small artery structural changes after Ang II infusion were the so-called eutrophic remodeling (unchanged media cross-sectional area).[21] A role of AT_1 receptors in the Ang II effects reported here is supported by previous data that demonstrated that ACE inhibition or antagonism of AT_1 receptors prevented or reversed hypertensive changes in resistance artery structure.[22]

Rosiglitazone used alone slightly increased BP. TZDs may have direct vascular effects mediated via activation of PPAR-γ and systemic effects on BP that could be in part PPAR-γ independent and unrelated to the renin-angiotensin-aldosterone

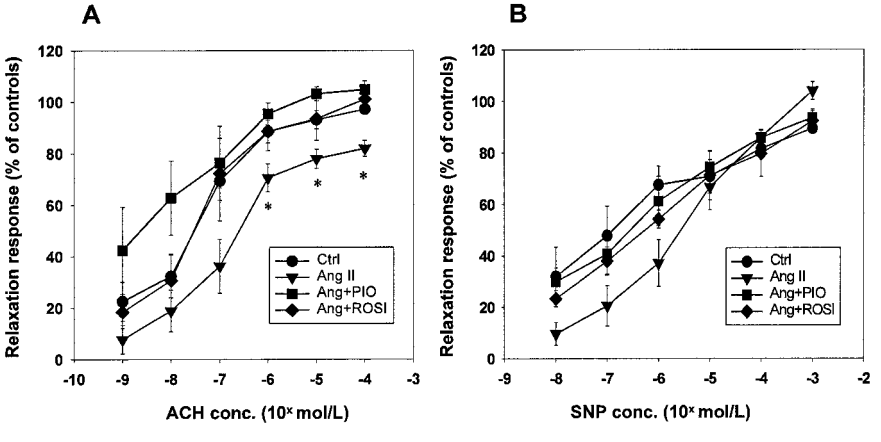


Figure 2. Endothelium-dependent relaxation in response to acetylcholine (A; ACH) and endothelium-independent relaxation in response to SNP (B) in mesenteric arteries of Ang II–infused rats treated without or with pioglitazone (PIO) or rosiglitazone (ROSI) for 7 days. Results are mean±SEM (n=5 to 6 per group). Relaxation is expressed as percent increase in intraluminal diameter after precontraction with 10^{-5} mol/L norepinephrine. *$P<0.05$ vs control (Ctrl). Conc. indicates concentration.

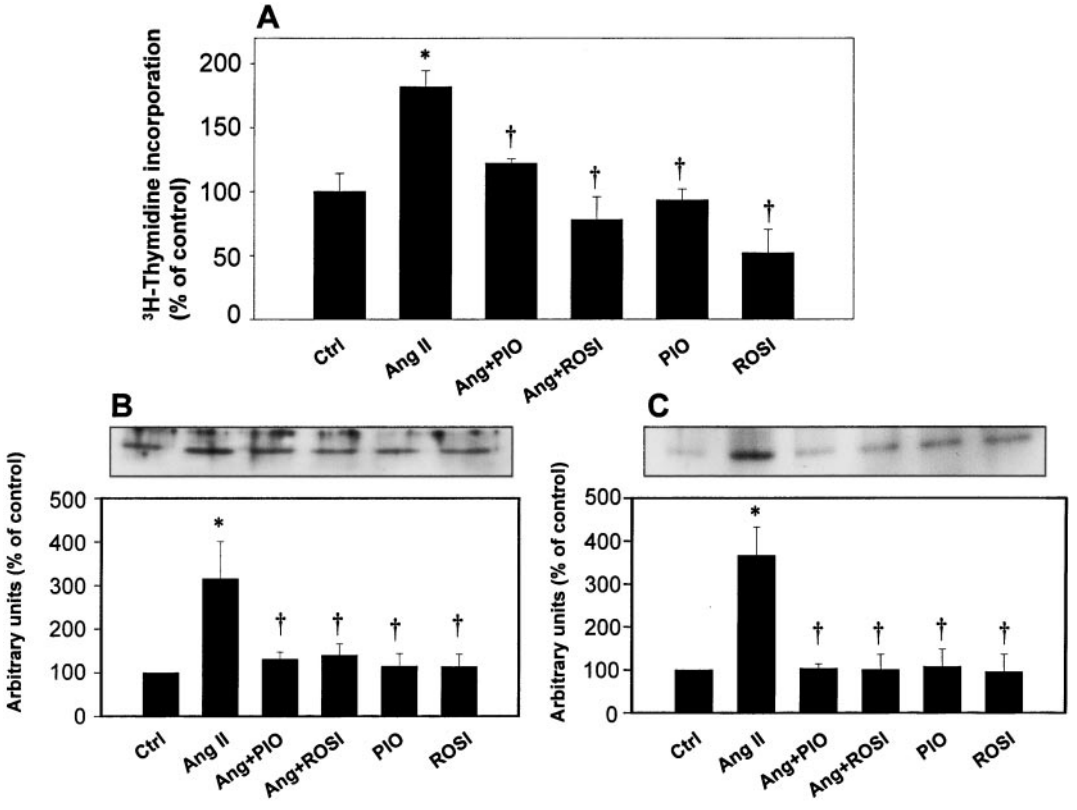


Figure 3. A, ^{3}H-thymidine incorporation into DNA (% of control) in mesenteric arteries of Ang II–infused rats with or without pioglitazone (PIO) or rosiglitazone (ROSI) after 7-day treatment. Results are mean±SEM, n=6. *P<0.05 vs control, †P<0.05 vs Ang II group. B, Representative Western blot of cyclin D1 in mesenteric arteries of Ang II–infused rats with or without PIO or ROSI after 7-day treatment. Results are mean±SEM, n=4. *P<0.05 vs control, †P<0.05 vs Ang II group. C, Representative Western blot of cdk4 in mesenteric arteries as in Figure 2B. Results are mean±SEM, n=4. *P<0.05 vs control, †P<0.05 vs Ang II group. Ctrl indicates control.

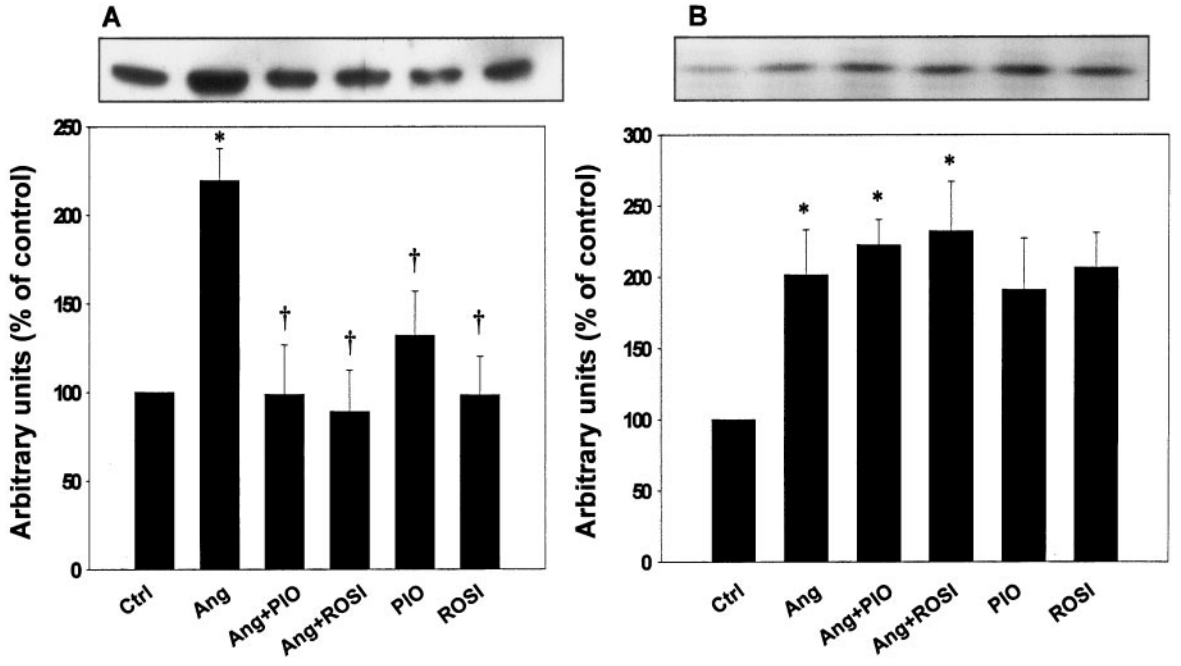
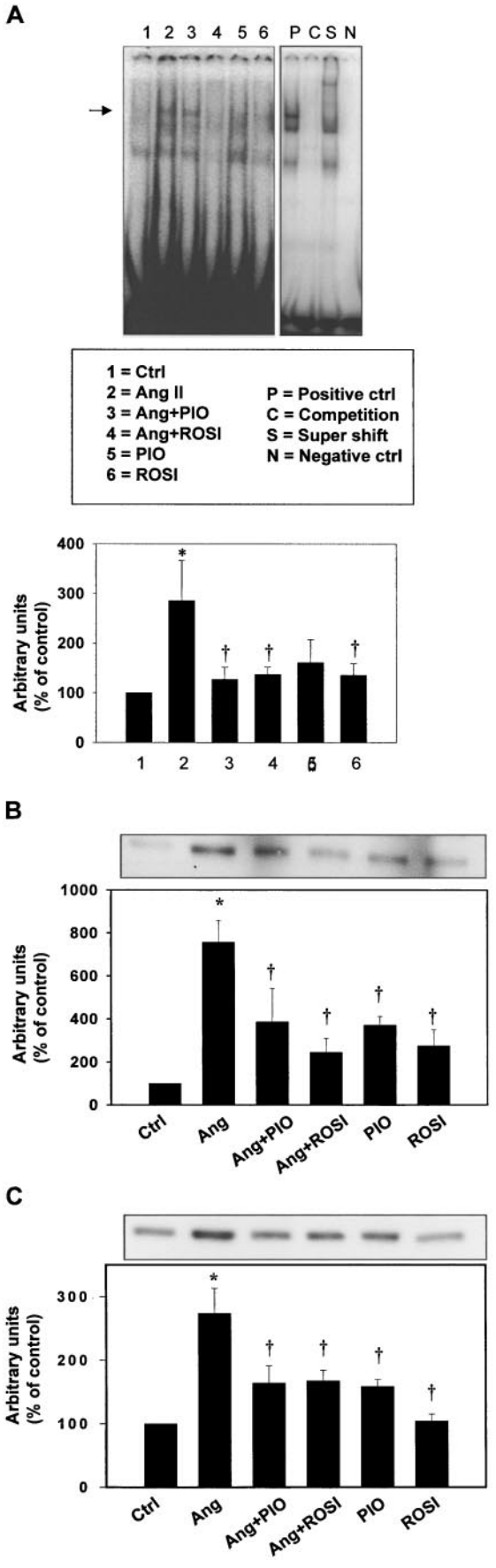


Figure 4. A, Representative Western blot of AT_1 receptors in mesenteric arteries of Ang II–infused rats with or without pioglitazone (PIO) or rosiglitazone (ROSI) after 7 day-treatment. Results are mean±SEM, n=4. *P<0.05 vs control, †P<0.05 vs Ang II group. B, Representative Western blot of AT_2 receptors in mesenteric arteries as in Figure 3A. Results are mean±SEM from 4 rats. *P<0.05 vs control. Ctrl indicates control.



system.[23] TZDs are insulin-sensitizing agents and may exert water- and salt-retaining effects,[24,25] and they could have other renal actions[26] that contribute to BP elevation. In our previous study,[27] PPAR-γ expression increased with age during development of hypertension, whereas it did not change in the present study in Ang II–infused rats despite the BP rise. Thus, expression of vascular PPAR-γ may have effects on vascular remodeling in hypertension that are independent of BP levels.

Pioglitazone and rosiglitazone protect against impairment of endothelial function associated with insulin resistance.[9,10] Mechanisms whereby TZDs improved endothelial dysfunction of resistance arteries of Ang II–infused rats could include attenuation of Ang II–induced oxidative stress[28,29] secondary to downregulation of AT_1 receptors, resulting in less nitric oxide degradation. We recently observed that pioglitazone and rosiglitazone decreased oxidative stress in blood vessels of Ang II–infused rats (unpublished data). An effect on agonist-mediated calcium uptake into VSMCs,[10] which would tilt the balance of constriction and relaxation in favor of the latter, could also play a role. Decreased BP could also contribute to improvement of endothelial dysfunction, but hydralazine, which lowered BP, had no effect in the present experiments, which suggests that BP lowering did not participate importantly in these findings.

Expression of PPAR-γ was thought to be limited primarily to adipose tissue and regulation of lipid metabolism. However, in the present study, neither of the TZDs had any effect on plasma cholesterol, triacylglycerol, or free fatty acid concentrations. Inflammation is an important mechanism in the progression of atherosclerosis. PPAR-γ activators blunt macrophage activation, as demonstrated by inhibition of gelatinase B (MMP-9), inducible nitric oxide synthase activity, and tumor necrosis factor-α release.[6,30] Activation of PPAR-γ in human endothelial cells can inhibit cell proliferation, modulate plasminogen activator inhibitor-1 expression, reduce endothelin-1 production, and induce apoptosis.[31] Endothelial cell PPAR-γ activation may inhibit activator protein-1 and NF-κB pathways that regulate expression of adhesion molecules. PPAR-γ activators may protect the vasculature by inhibiting the migration of monocytes into the vessel wall through inhibition of upregulation of adhesion molecules.[32] In the present study, both PPAR-γ agonists abrogated upregulation of transcription factor NF-κB and adhesion molecules, in agreement with previous reports.[6,33]

Our results have important implications for the clinical use of PPAR-γ ligands. In addition to playing a role in adipocyte differentiation, we demonstrate that TZDs have direct effects on the vascular wall. These vascular effects could be PPAR-γ mediated or PPAR-γ independent.[34] Together with evidence that dominant negative mutations in human PPAR-γ are associated not only with severe insulin resistance and diabetes mellitus but also with hypertension,[35] this suggests that use of TZDs to

Figure 5. A, Top: Representative NF-κB activity in aorta. Bottom: Results are mean±SEM from 3 rats. *$P<0.05$ vs control, †$P<0.05$ vs Ang II group. B, Representative Western blot of VCAM-1 in mesenteric arteries. Results are mean±SEM from 4 rats. *$P<0.05$ vs control, †$P<0.05$ vs Ang II group. C, Representative Western blot of PECAM in mesenteric arteries. Results are mean±SEM from 4 rats. *$P<0.05$ vs control, †$P<0.05$ vs Ang II group. PIO indicates pioglitazone; ROSI, rosiglitazone; and Ctrl, control.

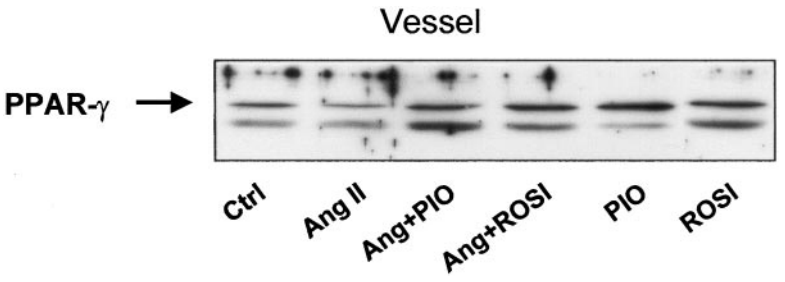


Figure 6. Western blot of PPAR-γ in mesenteric arteries. Data shown are representative of results of 4 experiments. Ctrl indicates control; PIO, pioglitazone; and ROSI, rosiglitazone.

activate PPAR-γ may represent an approach to protect the vasculature in hypertension. TZDs may be promising therapeutic agents not only to control metabolic abnormalities in diabetes but also for prevention and/or treatment of hypertension, particularly when associated with insulin resistance or diabetes mellitus.

Acknowledgments

This work was supported by grant 13570 (to Dr Schiffrin) and a group grant to the Multidisciplinary Research Group on Hypertension, both from the Canadian Institutes of Health Research (CIHR). Dr Diep was supported by a postdoctoral fellowship from CIHR. We are grateful to Suzanne Diebold, Marie-France Lavoie, André Turgeon, and Karim Benkirane for excellent technical assistance.

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