Angiotensin II Relaxes Microvessels Via the AT₂ Receptor and Ca²⁺-Activated K⁺ (BKCa) Channels

Christiana Dimitropoulou, Richard E. White, Leslie Fuchs, Hanfang Zhang, John D. Catravas, Gerald O. Carrier

Abstract—Angiotensin II (Ang II) is one of the most potent vasoconstrictor substances, yet paradoxically, Ang II may dilate certain vascular beds via an undefined mechanism. Ang II–induced vasoconstriction is mediated by the AT₁ receptor, whereas the relative expression and functional importance of the AT₂ receptor in regulating vascular resistance and blood pressure are unknown. We now report that Ang II induces relaxation of mesenteric microvessels and that this vasodilatory response was unaffected by losartan, an AT₁ receptor antagonist, but was inhibited by PD123,319, a selective antagonist of AT₂ receptors. In addition, reverse transcriptase–polymerase chain reaction studies revealed high amounts of AT₂ receptor mRNA in smooth muscle from these same microvessels. Ang II–induced relaxation was inhibited by either tetraethylammonium or iberiotoxin, suggesting involvement of the large-conductance, calcium- and voltage-activated potassium (BKCa) channel. Subsequent whole-cell and single-channel patch-clamp studies on single myocytes demonstrated that Ang II increases the activity of BKCa channels. As in our tissue studies, the effect of Ang II on BKCa channels was inhibited by PD123,319, but not by losartan. In light of these consistent findings from tissue physiology, molecular studies, and cellular/molecular physiology, we conclude that Ang II relaxes microvessels via stimulation of the AT₂ receptor with subsequent opening of BKCa channels, leading to membrane repolarization and vasodilation. These findings provide evidence for a novel endothelium-independent vasodilatory effect of Ang II. (Hypertension. 2001;37:301-307.)

Key Words: angiotensin II ▪ receptors, angiotensin ▪ potassium channels ▪ patch-clamp techniques

Many complications of hypertension and congestive heart failure are ameliorated by interdiction of the renin-angiotensin system, and agents that attenuate the effects of angiotensin II (Ang II) are now a first-line pharmacological antihypertensive intervention. Ang II induces constriction, hypertrophy, and proliferation of vascular smooth muscle via the AT₁ receptor. It is generally assumed that the therapeutic effects of AT₁ antagonists are due to direct receptor blockade; however, a secondary effect of these agents is increased plasma levels of Ang II,¹ which may then activate AT₂ receptors. This receptor bears only 34% sequence homology to the AT₁ receptor²,³ and mediates growth inhibition⁴ and apoptosis⁵ of vascular smooth muscle. In contrast, very little is known about the role of AT₂ receptors in regulating blood pressure. Both Ang II receptors are expressed in the vasculature, but AT₂ receptor expression is heterogeneous with respect to vascular bed, species, and developmental stage.⁶ Nonetheless, evidence suggests that AT₂ receptors modulate vascular contractility.⁷ AT₂ receptors mediate endothelium-dependent vasodilation of renal arterioles.⁷ Furthermore, AT₂-deficient mice exhibit an increased pressor response to Ang II,⁸ whereas overexpression of AT₂ receptors enhances Ang II–induced endothelium-dependent vasodilation.⁹ These findings suggest that AT₂ receptors mediate Ang II–induced vascular relaxation; however, the cellular/molecular basis of Ang II–induced vasodilation is not clearly defined, nor has an effector mechanism been identified. The purpose of the present study was to investigate the expression and physiological role of AT₂ receptors in the microvasculature. We now report significant expression of AT₂ receptors in mesenteric microvessels from adult rats and also demonstrate that Ang II relaxes these vessels via stimulation of the AT₂ receptor with subsequent opening of BKCa channels, leading to membrane repolarization and vasodilation. These findings provide evidence for an endothelium-independent vasodilatory effect of Ang II on vascular smooth muscle cells and may help to explain the salutary effects of AT₁ receptor antagonists on the cardiovascular system, (eg, reduced blood pressure and infarct size¹⁰ due to “indirect” stimulation of AT₂ receptors).

Methods

Isolated Microvessel Preparation
Fourth-order mesenteric arterial branches (200 to 300 μm in diameter) were isolated microscopically from male Sprague-Dawley rats

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From the Department of Pharmacology and Toxicology (C.D., R.E.W., L.F., J.D.C., G.O.C.) and the Vascular Biology Center (L.F., H.Z., J.D.C.), Medical College of Georgia, Augusta. Correspondence to Dr Gerald O. Carrier, Department of Pharmacology and Toxicology, Medical College of Georgia, 1120 15th St, Augusta, GA 30912-2300. E-mail ggcarrier@mail.mcg.edu © 2001 American Heart Association, Inc.
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(aged 14 to 16 weeks) in accordance with guidelines of the American Physiological Society for the humane treatment of experimental animals and prepared for measurement of intraluminal diameter by video dimension analysis as described previously. \(^1^3\) Vessels were allowed to equilibrate for 30 minutes and were preconstricted to \(\sim45\%\) of their resting diameter with endothelin-1 (ET-1). After the constriction reached a steady state level, a complete concentration-response relaxation to Ang II was performed. In additional vessels a concentration-response relationship for Ang II was measured in the presence of tetraethylammonium (TEA), ibotenic acid (IBTX), losartan, or PD123,319.

**Reverse Transcriptase–Polymerase Chain Reaction**

Smooth muscle cells from 5 mesenteric arteries for each RNA isolation (n=15 rats, 3 RNA isolations) were harvested and pooled for total RNA measurement. As a negative control, RNA was also extracted from rat liver. Total RNA was isolated with the use of Trizol Reagent (GIBCO BRL). Phase separation was achieved by addition of chloroform, and RNA was precipitated from the aqueous phase with isopropyl alcohol. The amount of RNA was determined spectrophotometrically at A\(_{260}\). Total RNA (1 to 1.5 \(\mu\)g) was treated with DNase I (GIBCO BRL) for 15 minutes at room temperature and reverse transcribed (RT) with oligo(dT) using SuperScript (GIBCO BRL). Aliquots of the RT products were amplified with \(Taq\) DNA polymerase (GIBCO BRL) with the use of gene-specific primers. Reverse transcriptase–polymerase chain reaction (RT-PCR) was performed as described previously with the use of primers derived from published cDNA sequences of the AT\(_1\)B (accession X64052) and AT\(_2\) receptor (accession D16640). Primer sequences for AT\(_1\)B were 5'-GCC ATT ATC GCT GAC TG A-3' (forward) and 5'-CTG CCT AGC CAA ATG GGT CCT C-3' (reverse), and the final PCR product was 446 bp in length. Primer sequences for the AT\(_2\) receptor were 5'-GGA GCG AGC ACA GAA TT GGA-3' (forward) and 5'-TGC CCA GAG AGG AAG GGT TGC C-3' (reverse), and the final PCR product was 446 bp in length. PCR negative controls were (1) amplification of \(H_2 O\) and (2) non-RT parallel with the RT reaction but without adding the RT enzyme. The samples that were obtained from the same RNA, processed in 3 separate RNA samples from mesenteric arterial SMC. 

**Path-Clamp Studies**

Single myocytes were isolated by a modification of a procedure described previously, \(^1^3\) and potassium channel activity was recorded in either the whole-cell (amphoterin perforated patch) configuration or from cell-attached or inside-out patches as described previously. \(^1^4\) Briefly, for cell-attached patches several drops of cell suspension were placed in a recording chamber containing the following (mmol/L): 140 KCl, 0.1 CaCl\(_2\), 10 HEPES, and 30 glucose (pH 7.4; 22°C to 25°C). Activity of single potassium channels was recorded in cell-attached patches by filling the patch pipette (2 to 5 M\(\Omega\)) with Ringer’s solution, as follows (mmol/L): 110 NaCl, 5 KCl, 1 MgCl\(_2\), 2 CaCl\(_2\), and 10 HEPES. In experiments on inside-out patches, the bathing solution exposed to the cytoplasmic surface of the membrane consisted of the following (mmol/L): 60 K\(_2\)SO\(_4\), 30 KCl, 2 MgCl\(_2\), 0.16 CaCl\(_2\), 1 BAPTA (10\(^{-7}\) M Ca\(^{2+}\)), 10 HEPES, 5 ATP, and 10 glucose (pH 7.4; 22°C to 25°C). The pipette solution was the same as Ringer’s solution described above. Current voltage relations were obtained from whole-cell or single-channel amplitudes at potentials between -50 and +50 mV, and single-channel conductance was calculated from the slope of the current-voltage relationship fitted by linear regression. Average channel activity (NPo) in patches with multiple BK\(_{Ca}\) channels was determined as described previously. \(^1^4\)

**Drugs**

TEA was obtained from Aldrich. Ang II, dihydrothreitol, amphotericin B, glibenclamide, 4-aminopyridine, and ET-1 were purchased from Sigma Chemical. PD123,319 was obtained from Research Biochemical International, papain from Worthington Biochemical Corp, and losartan from DuPont-NEN.

**Statistical Analysis**

All data were expressed as mean±SE except data from tension studies, which were expressed as percentage of maximum relaxation. Statistical significance between 2 groups was evaluated with Student’s \(t\) test, and a 1-way ANOVA was performed to evaluate significance between multiple groups. A \(P\) value <0.05 was considered to reflect a significant difference.

**Results**

**Ang II Dilates Microvessels Via the AT\(_2\) Receptor**

Baseline intraluminal diameter of microvessels (intraluminal pressure=40 mmHg) was 226±12 \(\mu\)m (n >30). Vessels were preconstricted to \(\sim45\%\) of the original baseline diameter with ET-1 (diameter reduced from 229±14 to 126±8 \(\mu\)m). In the absence of Ang II, ET-1–induced contraction was maintained for >60 minutes. A complete concentration-response curve for Ang II was then obtained. A typical tracing of Ang II–induced microvascular relaxation is illustrated in Figure 1A. On average, Ang II (0.1 to 300 nmol/L) induced a concentration-dependent relaxation with a maximum of 72±5% (Figure 1B; n=19). Pretreating microvessels with N-nitro-l-arginine (0.1 mmol/L; 30 minutes) had no...
effect on Ang II–induced relaxation (78±6%; n=4). A similar response to Ang II (78±3%; n=5) was obtained in microvessels pretreated for 30 minutes with 10 μmol/L losartan, a selective AT1 receptor antagonist (Figure 1B). In contrast, Ang II induced only 31±6% relaxation (n=10; Figure 1B) in microvessels pretreated for 30 minutes with 100 nmol/L PD123,319, a selective AT2 receptor antagonist. Pretreatment with these blocking agents did not affect baseline intraluminal diameter (Table). These studies indicate involvement of the AT2 receptor in Ang II–induced vasodilation, and subsequent molecular studies were designed to verify expression of this protein in rat mesenteric microvessels.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control</th>
<th>PD123,319</th>
<th>Losartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>229±14</td>
<td>219±18</td>
<td>240±15</td>
</tr>
<tr>
<td>Endothelin</td>
<td>126±8</td>
<td>109±10*</td>
<td>126±14*</td>
</tr>
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Values are mean±SE. Neither PD123,319 nor losartan affected intraluminal diameters before or after endothelin treatment.

*Significant decrease in intraluminal diameter compared with baseline (before endothelin) conditions (P<0.05).

Figure 2. Ang II–induced relaxation of microvessels is mediated by potassium channels. A, Average concentration-response relationship for Ang II relaxation of mesenteric microvessels in the presence of 1 mmol/L TEA. After addition of 1 μmol/L Ang II had no effect, subsequent addition of 10 μmol/L acetylcholine induced significant relaxation of the vessels. Each point represents the mean±SE of 4 experiments. B, Average concentration-response relationship for Ang II relaxation of mesenteric microvessels in the presence of 100 nmol/L PD123,319. After addition of 1 μmol/L Ang II had no effect, subsequent addition of 10 μmol/L acetylcholine induced significant relaxation of the vessels. Each point represents the mean±SE of 4 experiments. C, Superimposed whole-cell current tracings from single mesenteric myocytes recorded with the perforated patch configuration. Cells were voltage-clamped at a holding potential of −50 mV, and currents were elicited by 100 ms depolarizing pulses to −40, −10, 20, or 50 mV before or 10 to 15 minutes after exposure to 100 nmol/L Ang II. In the right panel, the effect of subsequent addition of 1 mmol/L TEA is illustrated. Dashed line indicates baseline current. D, Complete current-voltage relationship for steady state outward current (holding potential=−50 mV) before and 10 to 15 minutes after addition of 100 nmol/L Ang II. The effect of subsequent addition of 1 mmol/L TEA on the same cell is also plotted.

Ang II Receptor mRNA

Representative gels of AT1B and AT2 receptor mRNA from isolated mesenteric microvascular smooth muscle cells analyzed by RT-PCR are provided in Figure 1C. Each isolation was examined microscopically to ensure against contamination with other cell types; nonetheless, it is possible that some minor degree of contamination may have been present. Analysis consistently detected AT2 receptor mRNA. In contrast, amplification of liver RNA did not reveal any bands for Ang II receptor mRNA. Absence or very low copy of these Ang II receptors in liver is consistent with previous studies, whereas mRNA for β-actin was well detected in liver by RT-PCR.

Ang II–Induced Vasodilation Involves K+ Channels

We have demonstrated previously that disrupting the gradient for potassium efflux with high extracellular [K+] inhibits potassium channel–mediated vasorelaxation. To investigate whether AT2 receptor–mediated vasodilation is dependent on K+ efflux, microvessels were preconstricted with 80 mmol/L K+ and then exposed to Ang II (data not shown). In microvessels preconstricted with ET-1, Ang II–induced relaxation was measured after a 30-minute pretreatment with a potassium channel inhibitor: 1 mmol/L TEA (n=4; Figure 2A) or 100 nmol/L IBTx (n=4; Figure
In the presence of these agents, even high concentrations of Ang II failed to produce significant relaxation. In contrast, subsequent treatment of microvessels with 10 μmol/L acetylcholine relaxed the microvessels 70±14% (TEA; n=4) or 73±10% (IBTx; n=4).

Ang II Increases Potassium Currents in Single Myocytes

Direct evidence that Ang II stimulated outward potassium currents in microvascular myocytes was obtained from whole-cell (perforated patch) patch-clamp recordings. Ang II (100 nmol/L) increased macroscopic outward current over the entire range of membrane voltages. For example, at +50 mV Ang II nearly tripled (287±35%; n=7; P<0.001) the steady state outward current. Representative tracings illustrating the effect of Ang II are provided in Figure 2C. The stimulatory effect of Ang II was reversed completely by subsequent treatment with 1 mmol/L TEA. A lower concentration of Ang II (10 nmol/L) nearly doubled (93±12% at +50 mV; n=3; P<0.05) steady state outward currents, and the effect was again abolished by 1 mmol/L TEA (decreased 27±3% below control values). The complete current-voltage relationship for these experiments is illustrated in Figure 2D. In contrast to TEA, neither 4-aminopyridine (1 mmol/L; n=3), a blocker of the delayed rectifier K⁺ channel, nor glibenclamide (10 μmol/L; n=3), a blocker of the ATP-sensitive K⁺ channel, affected Ang II–stimulated outward current (data not shown). These findings strongly suggested that the BKCa channel mediated Ang II–induced relaxation of microvessels, and subsequent single-channel studies were undertaken to prove this hypothesis.

Ang II Stimulates BKCa Channel Activity

Ang II stimulated the activity of single potassium channels in mesenteric myocytes. As illustrated in Figure 3A, there was minimal channel activity in cell-attached patches under control conditions (NPo<0.001 at +50 mV). However, channel activity was increased dramatically by 100 nmol/L Ang II (NPo 0.92; 15 minutes; Figure 3A), and this effect was concentration dependent (Figure 3B). Identification of this protein as the BKCa channel was demonstrated from experiments on cell-free inside-out patches in symmetrical (140 mmol/L) K⁺. Each point represents the mean±SE current of 3 to 5 patches, with the line fit by linear regression.

Figure 3. Ang II stimulates the activity of single BKCa channels in myocytes from mesenteric microvessels. A, Current tracings from the same cell-attached patch (+50 mV) before and 10 minutes after addition of 100 nmol/L Ang II. Channel openings are upward deflections from baseline (closed state, as indicated by dashed line. B, Average activity (NPo) of BKCa channels recorded from cell-attached patches before and 10 to 15 minutes after addition of either 6 (n=4), 60 (n=4), or 100 nmol/L (n=6) Ang II. *Significant increase in channel NPo compared with control level. C, Average current-voltage relationship for single-channel activity recorded from inside-out patches with symmetrical (140 mmol/L) K⁺. Each point represents the mean±SE current of 3 to 5 patches, with the line fit by linear regression.
centration of calcium at the cytoplasmic surface of the membrane from 100 nmol/L to 100 μmol/L produced a substantial increase in channel gating behavior (Figure 4, top panel). These experiments identify this protein as the high-conductance, Ca^{2+}-activated (BK_{Ca}) channel. In contrast to its effects on BK_{Ca} channels in cell-attached patches, addition of 100 nmol/L Ang II to the cytoplasmic surface of an inside-out patch had no effect on channel activity (n=3).

**AT_{2} Receptors Mediate Ang II Stimulation of BK_{Ca} Channels**

Ang II receptor antagonists were used to determine which receptor mediated the stimulatory effect of Ang II on BK_{Ca} channels. Channel activity stimulated by 100 nmol/L Ang II is illustrated in Figure 4 under control conditions (panel 2) or after a 30-minute pretreatment with 10 μmol/L losartan (panel 3). Blockade of AT_{2} receptors with losartan did not affect Ang II–induced channel activity. On average, control NPo was 0.001±0.002, and after exposure to 100 nmol/L Ang II NPo increased to 0.86±0.02 (n=4). Blockade of AT_{2} receptors, on the other hand, completely prevented the stimulatory effect of Ang II. In the presence of PD123,319 (100 nmol/L, 30 minutes), 100 nmol/L Ang II had no effect on BK_{Ca} channel activity (NPo PD123,319, <0.001; PD123,319+Ang II, <0.001; n=4; bottom panel).

**Discussion**

We have demonstrated that Ang II relaxes mesenteric microvessels via a mechanism involving the AT_{2} receptor and BK_{Ca} channel activity, and this mechanism of Ang II action on intact tissues was confirmed by molecular studies on isolated microvascular myocytes demonstrating (1) expression of AT_{2} receptor mRNA and (2) AT_{2} receptor–mediated stimulation of BK_{Ca} channel activity in cell-attached patches. These findings provide evidence for a novel endothelium–independent effect of Ang II on the microvasculature. Previous studies suggest that Ang II relaxes cerebral microvessels\textsuperscript{19,20} or renal afferent arterioles\textsuperscript{7} by an endothelium–dependent mechanism, probably involving release of bradykinin and endothelium-derived dilators (eg, NO).\textsuperscript{9,10} In the present study, however, pretreating mesenteric microvessels with N-nitro-L-arginine did not affect Ang II–induced relaxation, suggesting that endothelium-derived NO does not play a role in the response of this vascular bed to Ang II. More directly, in the absence of endothelium Ang II clearly stimulated activity of BK_{Ca} channels in isolated myocytes.

Previous studies indicated that Ang II stimulates both whole-cell\textsuperscript{21} and single-channel\textsuperscript{22} potassium currents in cultured neurons via the AT_{2} receptor; however, this is the first study on the effects of Ang II on K^{+} channels in smooth muscle cells. Our studies demonstrate that Ang II increases both whole-cell and single-channel BK_{Ca} currents in mesenteric myocytes. Instead of traditional whole-cell recordings that require dialysis of the cytoplasm with exogenous calcium buffers, we used the perforated patch configuration to obtain whole-cell currents from “metabolically intact” myocytes. These findings indicated that Ang II increases a TEA-sensitive outward current in these cells, and subsequent single-channel studies revealed that this channel had a high conductance (>150 picoSiemens) and was stimulated by increasing “intracellular” calcium levels in inside-out patches. Therefore, we have identified this protein as the BK_{Ca} channel that is highly expressed in vascular smooth muscle and other cell types. Like other vascular smooth muscle cells, myocytes from mesenteric microvessels possess substantial outward K^{+} currents composed primarily of K^{+} efflux through BK_{Ca} channels.\textsuperscript{11} Because of their large conductance and high density of expression, these channels help to set and maintain the resting membrane potential of vascular smooth muscle.\textsuperscript{23} When intracellular [Ca^{2+}] levels increase during contraction, BK_{Ca} channels provide an important repolarizing negative feedback mechanism that helps to reverse active contraction. Given the importance of BK_{Ca} channels in regulating vascular tone, these proteins constitute a powerful effector mechanism that mediates microvascular relaxation induced by a variety of vasodilatory agents, eg, nitrovasodilators.\textsuperscript{11} Our studies indicated that microvascular relaxation required physiological gradients of [K^{+}] suitable for potassium efflux, suggesting involvement of potassium channels. Although several species of K^{+} channels are also expressed in vascular smooth muscle, we did not observe significant effects of Ang II on other channel species at the single-channel level. Moreover, neither glibenclamide (K_{ATP} channel antagonist) nor 4-aminopyridine (delayed rectifier channel antagonist) affected Ang II–stimulated whole-cell...
currents. In contrast, selective blockade of BK$_{Ca}$ channels (with either 1 mmol/L TEA or 100 nmol/L IBTx; Figure 2) abolished Ang II–induced relaxation. Although TEA can block several species of potassium channels, at this low concentration it exhibits selectivity for the BK$_{Ca}$ channel. IBTx, on the other hand, is a highly selective BK$_{Ca}$ channel antagonist. Moreover, our single-channel patch-clamp data clearly identified the BK$_{Ca}$ channel as a primary target of Ang II action in microvascular myocytes, and our findings that PD123,319 (but not losartan) inhibited this stimulatory effect of Ang II further implicate the BK$_{Ca}$ channel as an effector molecule for AT$_2$ receptor–mediated vasodilation. Although our findings clearly demonstrate an endothelium-independent effect of Ang II on microvascular myocytes, the vasodilatory response to Ang II in vivo would probably involve both endothelium-dependent and -independent mechanisms. In either case, our data obtained from intact tissues or single myocytes indicate that BK$_{Ca}$ channels expressed in microvascular smooth muscle cells are the critical effector molecules involved in AT$_2$ receptor–mediated relaxation of microvessels.

The signaling process linking AT$_2$ receptors to BK$_{Ca}$ channels in vascular smooth muscle is poorly understood. For example, metabolites of arachidonic acid might play a role in the response of BK$_{Ca}$ channels to Ang II in mesangial cells; however, it is unclear whether the response of BK$_{Ca}$ channels in these cells is mediated via AT$_1$ and/or AT$_2$ receptors. Therefore, it is difficult to draw strict comparisons between these 2 studies on different cell types and species. Nonetheless, because arachidonic acid metabolites open BK$_{Ca}$ channels in other arteries, a potential role of arachidonic acid in mediating the response of mesenteric microvessels to Ang II remains a possibility. Alternatively, BK$_{Ca}$ channels could be opened indirectly by Ang II–stimulated intracellular calcium. Although we have not tested this hypothesis conclusively, we do not believe that direct activation by calcium plays a major role because of the following: (1) Ang II induces vasodilation; therefore, the putative increase in calcium would have to be minimal and probably localized to the more peripheral regions of the cytoplasm near the BK$_{Ca}$ channels. Such a “calcium-spark” model is possible, but we are unaware of any studies suggesting that Ang II stimulates such a mechanism in microvessels. (2) Ang II produced no obvious shift in the voltage sensitivity of outward currents, whereas increased [Ca$^{2+}$], shifts the sensitivity of BK$_{Ca}$ channels to more negative potentials. In contrast, the effect of Ang II appears to be due mainly to increased current amplitude rather than increased voltage sensitivity. In contrast to the aforementioned mechanisms, it is clear that cyclic nucleotide–dependent vasodilators open BK$_{Ca}$ channels in vascular smooth muscle. In the present study, however, inhibitors of either the cAMP- or cGMP-dependent protein kinases had no effect on Ang II–stimulated BK$_{Ca}$ channel activity (data not shown). These data suggest that a more novel mechanism of action underlies the effect of Ang II in microvessels; however, further experiments are necessary to elucidate the transduction mechanism coupling AT$_2$ receptors to BK$_{Ca}$ channels.

It is clear that AT$_2$-induced vasodilation affects blood pressure. Animals lacking AT$_2$ receptors exhibit an enhanced pressor response to Ang II, whereas overexpression of AT$_2$ receptors antagonizes AT$_1$ receptor–mediated pressor effects. AT$_2$ receptor–mediated vasodilation, particularly of microvessels, may serve as a negative feedback mechanism to counterbalance the potent vasoconstrictor effect of AT$_1$ receptor activation. For example, Ang II levels are increased during exercise, and AT$_2$ receptor–mediated dilation of precapillary vessels might help to offset potentially dangerous effects of diminished capillary perfusion in face of excessive AT$_1$ receptor stimulation. Therapeutically, it seems clear that AT$_2$ receptors mediate salutary responses. For example, AT$_2$ receptor stimulation may play a part in the antihypertensive effects of AT$_1$ receptor antagonists, which increase plasma Ang II levels. In addition, our proposed “endothelium-independent” vasodilatory effect of Ang II could constitute a protective vasodilatory mechanism to preserve tissue perfusion when the endothelium is damaged as a result of atherosclerosis and/or hemodynamic stress. Interestingly, activation of AT$_2$ receptors reduces infarct size. The present findings are the first to provide direct experimental evidence for a novel molecular effector (the BK$_{Ca}$ channel) that can mediate endothelium-independent relaxation of vascular smooth muscle via Ang II stimulation of the AT$_2$ receptor. Future studies will identify and characterize the postreceptor signal transduction cascade stimulated by Ang II in these microvessels.

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