Defective Modulation of Angiotensin II–Induced Renal Vasoconstriction in Hypertensive Rats

Edwin K. Jackson, William A. Herzer

Abstract In a previous study we observed that the ability of intravenous infusions of prostaglandin I\(_2\) (PGI\(_2\)) to attenuate vasoconstriction caused by intravenous infusions of angiotensin II was reduced in the renal but not mesenteric vasculature of spontaneously hypertensive rats (SHR). One objective of the current study was to determine whether the renal defect in the angiotensin II/prostaglandin I\(_2\) interaction in SHR could be confirmed even when confounding hemodynamic changes induced by intravenous infusions of prostaglandin I\(_2\) were avoided. The second objective was to determine whether abnormal modulation of angiotensin II–induced renal vasoconstriction was present even in SHR that were maintained normotensive from an early age. Four-week-old SHR and normotensive Wistar-Kyoto rats were randomized to receive either normal drinking water or drinking water containing captopril (100 mg/kg per day). At 14 to 18 weeks of age, rats were pretreated with indomethacin to block the production of endogenous prostaglandin I\(_2\), and changes in mesenteric and renal vascular resistances induced by suprarenal/supramesenteric aortic infusions of angiotensin II (10, 30, and 100 ng/kg per minute) were elicited in the presence and absence of aortic infusions of prostaglandin I\(_2\) (0.1 and 0.3 \(\mu\)g/kg per minute). Data were analyzed globally using four- and three-factor ANOVAs. The ability of prostaglandin I\(_2\) to attenuate the renal vasoconstrictor response to angiotensin II was strain specific (\(P=.0138\)), and this strain-specific interaction was not influenced by chronic treatment with captopril (\(P=.3526\)). In Wistar-Kyoto rats, prostaglandin I\(_2\) attenuated the renal response to angiotensin II (\(P=.0071\)) but not so in SHR (\(P=.3930\)). Prostaglandin I\(_2\) also attenuated the response to angiotensin II in the mesentry (\(P=.0306\), but the angiotensin II/prostaglandin I\(_2\) interaction in this vascular bed was not defective in SHR. We conclude that the SHR has a genetically acquired, kidney-selective defect in the angiotensin II/prostaglandin I\(_2\) interaction. (Hypertension. 1994;23:329-336.)

Key Words • epoprostenol • angiotensin II • rats, inbred SHR • vasoconstriction

In a recent study, we examined the ability of intravenous infusions of prostaglandin I\(_2\) (PGI\(_2\)) to attenuate the systemic hemodynamic effects, the renal vasoconstricting actions, and the mesenteric vasoconstricting effects of intravenous infusions of angiotensin II (Ang II) in both spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto (WKY) rats. This study suggested that the ability of PGI\(_2\) to attenuate the vascular response to Ang II was diminished in the kidneys of SHR, whereas the overall hemodynamic effects and mesenteric vasoconstricting effects of Ang II were attenuated similarly by PGI\(_2\) in SHR versus WKY rats.

The advantage of the experimental design used in our previous study was that it permitted an examination of the Ang II/PGI\(_2\) interaction in the entire cardiovascular system as well as in specific organ beds of naive SHR and WKY rats. However, one disadvantage of the previous study was that intravenous administration of PGI\(_2\) caused profound systemic hypertension that may have confounded the interpretation. Also, the SHR used in our previous study were allowed to develop hypertension so that any renal defect in the Ang II/PGI\(_2\) interaction may have been caused by hypertension-induced kidney damage rather than being a primary, genetically acquired trait.

The purpose of the present study was to further test the hypothesis that SHR have a genetically acquired, kidney-selective defect in the Ang II/PGI\(_2\) interaction. In the present investigation, a study design was used that allowed a comparison of the ability of PGI\(_2\) to modulate the mesenteric and renal vascular responses to Ang II while avoiding marked PGI\(_2\)-induced hypertension. This study design was applied to both naive SHR and WKY rats as well as SHR and WKY rats that were treated from 4 weeks of age with high doses of captopril to prevent hypertension-induced renal damage in the SHR. The results of this study are consistent with the hypothesis that SHR have a genetically acquired, kidney-selective defect that gives rise to a diminished ability of PGI\(_2\) to attenuate the renal vascular response to Ang II.

Methods

Four-week-old SHR and WKY rats were obtained from Taconic Farms. Rats were kept in an animal care facility with a 12-hour light/dark cycle (7 AM to 7 PM), ambient temperature of 22°C, and relative humidity of 55%. Animals were fed Wayne Rodent Blox 8604 (135 mEq sodium/kg and 254 mEq potassium/kg) and were randomly assigned to receive either normal drinking water or drinking water to which captopril was added to provide a dosage of 100 mg/kg per day. We have shown previously that this dosage of captopril reliably prevents the development of hypertension in SHR. Animals were studied when they were between 14 and 18 weeks of age.
study was approved by the Institutional Animal Care and Use Committee.

To block the synthesis of endogenous prostaglandins, we pretreated rats with three doses of indomethacin (5 mg/kg, suspended in olive oil and administered subcutaneously 24 hours, 12 hours, and immediately before surgery). This approach permitted an evaluation of the effects of exogenous PGI2 in SHR and WKY rats with similarly low baseline levels of endogenous PGI2. Rats were anesthetized with an intraperitoneal injection of 50 mg/kg pentobarbital. After induction of anesthesia, the animals were placed on a preheated Delcath Phase Isothermal Pad (Brainstem Tree, Inc). A heat lamp was positioned above the animal, a rectal temperature probe was inserted, and body temperature was monitored with a digital thermometer (Physiostemp Instruments, Inc). The distance of the heat lamp from the animal was adjusted to maintain body temperature at 37±0.5°C.

After the rat’s trachea was cannulated with polyethylene tubing (PE-240) to facilitate respiration, a catheter (PE-50) was inserted into the left jugular vein, and an infusion of 0.9% saline was begun at 100 μL/min. A PE-50 cannula was placed in the left carotid artery and this catheter was attached to a digital blood pressure analyzer (Micro-Med, Inc) for continuous measurement of mean arterial blood pressure and heart rate.

The animal’s abdominal cavity was exposed with a midline incision, and the left renal artery and superior mesenteric artery were carefully freed from surrounding tissue. A transit-time blood flow probe was placed around each vessel (Transonic Systems), and the blood flowmeter (model T206, Transonic Systems). Interference between the two flow probes was prevented by the internal synchronization features on the blood flowmeter. Next, two 32-gauge needles attached to silicone elastomer tubing were inserted into the abdominal aorta such that the tips of the needles were just proximal to the left renal artery and superior mesenteric artery.

Regarding the accuracy of the transit-time flow probes, Transonic Systems bench-calibrated the flow probes against water and specified an in vivo accuracy of better than ±20%. In pilot experiments, we measured renal blood flow using clearance methods and simultaneously measured renal blood flow with transit-time flow probes. On average the two methods gave values within 5% of each other. Extensive in vivo validation studies by Welch et al indicate that the small-animal transit-time flow probes provide accuracy well within the manufacturer’s specifications.

After completion of the surgical procedure, the jugular infusion of saline was stopped and replaced with an infusion of saline through one of the intra-arterial catheters in the aorta (80 μL/min). An infusion of 0.1 mol/L Na2CO3 (20 μL/min) was initiated into the second intra-arterial catheter. All rats then were administered captopril (30 mg/kg IV) through the jugular catheter to block the synthesis of endogenous Ang II.

This was necessary so that the effects of exogenous Ang II could be observed in the absence of changes in levels of endogenous Ang II.

After a 60-minute stabilization period the protocol was begun, involving three experimental periods separated by 30 minutes. At the beginning of each experimental protocol, the intra-arterial infusion of 0.1 mol/L Na2CO3 was either maintained or switched to an infusion of either 0.1 or 0.3 μg/kg per minute PGI2 (the order of treatments was randomized). PGI2 was dissolved in 0.1 mol/L Na2CO3 infused at 20 μL/min. Approximately 5 minutes into the infusion of PGI2, regional blood flows and arterial blood pressure and heart rate were recorded. Arterial blood pressure and heart rate were time averaged for 1 minute (arterial blood pressure sampling rate=1100/s with an 82% duty cycle), and organ blood flows were recorded from the digital display of the flowmeter.

While the PGI2 infusion was continued, the intra-arterial saline infusion was switched to an infusion of Ang II (10 ng/kg per minute). Ang II was dissolved in saline and infused at 80 μL/min. Approximately 5 minutes into the combined infusions of PGI2 and Ang II, all measurements were recorded. While the PGI2 infusion was maintained, the Ang II dose was increased to 30 and then 100 ng/kg per minute (approximately 5 minutes at each dose), and all measurements were repeated just before the end of each dose of Ang II. Tachyphylaxis to Ang II was not observed in either strain during the 5-minute infusions of Ang II. Infusions of PGI2 and Ang II were terminated, and infusions of 0.1 mol/L Na2CO3 and 0.9% saline were restored. This procedure was repeated during two more periods separated by 30 minutes with different doses of PGI2 used in each period.

A PGI2 stock solution was prepared in absolute ethanol and stored under nitrogen at ~75°C. A few milligrams of Na2CO3 was added to the stock solution of PGI2 to maintain a high pH. Solutions used in the experiments were prepared daily by placing a few microliters of stock into an appropriate volume of 0.1 mol/L Na2CO3 and diluting further with 0.1 mol/L Na2CO3 as required. An equal amount of ethanol was diluted into the 0.1 mol/L Na2CO3 that was infused between the PGI2 infusions. A stock solution of Ang II was prepared in a buffer solution, divided into aliquots, and stored at ~75°C. On each day a fresh aliquot of Ang II stock solution was thawed, a few microliters of stock was added to an appropriate volume of 0.9% saline, and further dilutions were made in 0.9% saline as required. An equal amount of buffer solution was diluted into the 0.9% saline that was infused between the Ang II infusions. Both PGI2 and Ang II were obtained from Sigma Chemical Co.

Data were analyzed statistically by four-factor ANOVA in which the factors were (1) chronic treatment with captopril or not, (2) rat strain, (3) dose of PGI2, and (4) dose of Ang II. The latter two factors were treated as repeated-measures factors (ie, factors 3 and 4 were nested under rat strain). A separate three-factor ANOVA was conducted for each rat strain if an interaction among rat strain, dose of PGI2, and dose of Ang II was detected. In the three-factor ANOVA the factors were (1) chronic treatment with captopril or not, (2) dose of PGI2, and (3) dose of Ang II. Again, the latter two factors were treated as repeated-measures factors. Statistical analysis was performed using the Number Crunchers Statistical System. Data are presented as mean±SEM.

Results

The Table lists mean arterial blood pressures, heart rates, renal blood flows, renal vascular resistances, mesenteric blood flows, and mesenteric vascular resistances for all four groups of animals before the infusions of Ang II, ie, in the presence of 0.0, 0.1, and 0.3 μg/kg per minute PGI2 but before the infusions of Ang II were initiated. Before the infusion of Ang II, arterial blood pressures were not significantly different during the three experimental periods in any of the four groups, although the highest dose of PGI2 did tend to decrease arterial blood pressure in the SHR receiving chronic captopril treatment. Also, PGI2 did not affect baseline renal blood flows or baseline renal vascular resistances in any of the four groups. PGI2 tended to increase baseline mesenteric blood flow and decrease mesenteric vascular resistance in all four groups, but this achieved statistical significance only for the mesenteric vascular resistance in WKY rats chronically treated with captopril.

Figs 1 through 4 illustrate the effects of Ang II on renal vascular resistance at each level of PGI2 in WKY...
Hemodynamic Parameters Before Infusion of Angiotensin II in Each Experimental Period (at Each Infusion Rate of Prostaglandin I₂)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WKY rats (n=10)</th>
<th>Prostaglandin I₂ Infusion Rate, μg/kg per minute</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (Vehicle)</td>
<td>0.1</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>85±5</td>
<td>80±5</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>346±9</td>
<td>353±13</td>
</tr>
<tr>
<td>RBF, mL·min⁻¹·kg⁻¹</td>
<td>36±4</td>
<td>36±3</td>
</tr>
<tr>
<td>RVR, mm Hg·mL⁻¹·min⁻¹·kg⁻¹</td>
<td>2.7±0.4</td>
<td>2.3±0.2</td>
</tr>
<tr>
<td>MBF, mL·min⁻¹·kg⁻¹</td>
<td>17±2</td>
<td>22±3</td>
</tr>
<tr>
<td>MVR, mm Hg·mL⁻¹·min⁻¹·kg⁻¹</td>
<td>5.8±0.8</td>
<td>4.1±0.6</td>
</tr>
</tbody>
</table>

WKY rats chronically treated with captopril (n=6)

| MABP, mm Hg              | 69±7                                 | 61±10                                         | 59±6                                          |
| HR, bpm                  | 377±14                               | 374±20                                        | 393±16                                        |
| RBF, mL·min⁻¹·kg⁻¹       | 30±4                                 | 24±4                                          | 22±3                                          |
| RVR, mm Hg·mL⁻¹·min⁻¹·kg⁻¹ | 2.5±0.3                             | 2.6±0.3                                       | 2.7±0.2                                       |
| MBF, mL·min⁻¹·kg⁻¹       | 14±4                                 | 21±4                                          | 29±8                                          |
| MVR, mm Hg·mL⁻¹·min⁻¹·kg⁻¹ | 5.5±0.9                             | 3.2±0.6*                                      | 2.6±0.5*                                      |

SHR (n=10)

| MABP, mm Hg              | 92±4                                 | 88±3                                          | 88±4                                          |
| HR, bpm                  | 360±5                                | 376±10                                        | 378±9                                          |
| RBF, mL·min⁻¹·kg⁻¹       | 27±3                                 | 24±2                                          | 25±3                                          |
| RVR, mm Hg·mL⁻¹·min⁻¹·kg⁻¹ | 3.8±0.5                             | 4.0±0.4                                       | 3.8±0.4                                       |
| MBF, mL·min⁻¹·kg⁻¹       | 9±1                                  | 13±2                                          | 13±2                                          |
| MVR, mm Hg·mL⁻¹·min⁻¹·kg⁻¹ | 12.1±1.6                            | 9.3±2.3                                       | 7.8±1.0                                       |

SHR chronically treated with captopril (n=6-7)

| MABP, mm Hg              | 87±7                                 | 78±6                                          | 86±4                                          |
| HR, bpm                  | 370±11                               | 374±11                                        | 368±7                                          |
| RBF, mL·min⁻¹·kg⁻¹       | 24±3                                 | 25±4                                          | 19±2                                          |
| RVR, mm Hg·mL⁻¹·min⁻¹·kg⁻¹ | 3.8±0.4                             | 3.8±0.7                                       | 3.7±0.4                                       |
| MBF, mL·min⁻¹·kg⁻¹       | 16±4                                 | 23±4                                          | 22±6                                          |
| MVR, mm Hg·mL⁻¹·min⁻¹·kg⁻¹ | 7.4±1.3                             | 4.6±1.0                                       | 4.0±0.6                                       |

WKY indicates Wistar-Kyoto rats; MABP, mean arterial blood pressure; HR, heart rate; bpm, beats per minute; RBF, renal blood flow; RVR, renal vascular resistance; MFB, mesenteric blood flow; MVR, mesenteric vascular resistance; and SHR, spontaneously hypertensive rats. Values are mean±SEM.

*P<.05 compared with vehicle by Fisher's least significant difference test.

To explore how the Ang II/PGI₂ pharmacologic interaction depended on rat strain, we reanalyzed the data according to rat strain using a three-factor ANOVA. In other words, the data from WKY rats (shown in Figs 1 and 2) were used to construct a three-factor ANOVA, and the data from SHR (shown in Figs 3 and 4) were used in a separate three-factor ANOVA. In the case of WKY rats, a highly significant statistical interaction between Ang II and PGI₂ was noted (P=.0071), whereas in SHR the statistical interaction between Ang II and PGI₂ was not significant (P=.3930). These statistical results clearly indicated the nature of the three-way interaction revealed by the four-factor ANOVA; ie, PGI₂ attenuated the effects of Ang II in WKY rats but not in SHR.
It is also important to note that with the four-factor ANOVA, the statistical interaction among captopril, rat strain, PGI$_2$, and Ang II was not significant ($P=0.3526$). Also, neither of the three-factor ANOVAs showed significant statistical interaction among captopril, PGI$_2$, and Ang II ($P=0.7172$ for WKY rats and $P=0.3881$ for SHR). These statistical results clearly indicated that chronic therapy with captopril did not restore in SHR the pharmacologic interaction between Ang II and PGI$_2$.

Figs 6 through 9 illustrate the effects of Ang II on mesenteric vascular resistance at each level of PGI$_2$ in WKY rats that did not receive chronic captopril treatment (Fig 6), in WKY rats that did receive chronic captopril treatment (Fig 7), in SHR that did not receive chronic captopril treatment (Fig 8), and in SHR that did receive chronic captopril treatment (Fig 9). The data illustrated in Figs 6 through 9 also were subjected to a global analysis using a four-factor ANOVA in which the factors were treatment or not.
with captopril, rat strain, dose of PGI₂, and dose of Ang II (Fig 10). This analysis revealed a significant two-way interaction between Ang II and PGI₂ (P=0.0306); ie, PGI₂ attenuated the responses to Ang II in the mesenteric vascular bed. Furthermore, the three-way interaction involving rat strain, PGI₂, and Ang II and the four-way interaction involving captopril, rat strain, PGI₂, and Ang II were not statistically significant (P=0.2006 and P=0.6450, respectively), indicating a lack of evidence that the pharmacologic interaction between PGI₂ and Ang II in the mesentery depended on rat strain.

**Discussion**

In two separate studies using different methodologies we have documented an increased renal responsiveness to intrarenal infusions of Ang II in adult SHR. In these studies, SHR were pretreated from an early age with captopril, a converting enzyme inhibitor, to prevent the development of hypertension.²⁻³ This approach allowed renal vascular responsiveness to be assessed in SHR with minimal hypertension-induced cardiovascular and renal changes and with baseline hemodynamic conditions similar to normotensive WKY rats. In a third study, also conducted in chronically captopril-treated SHR, we found that intravenous infusions of Ang II

![Graph showing mesenteric vascular resistance (MVR) as a function of infusion rate of angiotensin II (Ang II) in the presence and absence of infusions of prostaglandin I₂ (PGI₂) in normotensive, indomethacin-treated Wistar-Kyoto (WKY) rats. See Fig 10 for summary of statistical analysis.]
caused a greater increase in renal vascular resistance, whereas the vascular response in the mesenteric, carotid, and hindquarter vascular beds was normal. This latter study suggested that the increased vascular responsiveness to Ang II in SHR was a kidney-selective defect. Importantly, Chatziantoniou et al determined that renal vascular responses to bolus intrarenal injections of Ang II were enhanced in young and adult SHR that were allowed to develop hypertension. Most recently, an abstract by Wolff and Pettinger indicated that SHR have an enhanced renal vascular response to intrarenal bolus injections of Ang II in conscious animals. Thus, when taken together, currently available studies indicate that the SHR kidney has an enhanced responsiveness to Ang II regardless of (1) whether hypertension is allowed to develop or not, (2) age, (3) state of anesthesia, (4) whether Ang II is given intravenously or directly into the renal artery, and (5) whether Ang II is administered as a bolus injection or by steady-state infusion.

Because the enhanced renal vascular response to Ang II in SHR could at least in part explain the pathophysiology of genetic hypertension in SHR, it is important to elucidate the mechanism of this increased responsiveness to Ang II. In this regard, Chatziantoniou et al discovered that the differential renal vascular response to Ang II in SHR versus WKY rats was abolished by inhibition of prostaglandin biosynthesis with indomethacin, suggesting some involvement of prostanoids in the abnormal response in SHR. These results caused us to consider the hypothesis that a defective interaction between Ang II and PGI₂ could explain the enhanced renal responsiveness to Ang II.

In the current study, a renal-selective defect in the Ang II/PGI₂ interaction in SHR was confirmed even when confounding hemodynamic changes induced by intravenous infusions of PGI₂ were avoided by infusing PGI₂ into the aorta just proximal to the orifices of the superior mesenteric and left renal arteries. Also, the renal-selective defect in the Ang II/PGI₂ interaction was observed regardless of whether SHR were maintained normotensive with chronic administration of high doses of captopril or were allowed to develop hypertension. Although we did not measure systemic blood pressure chronically in the current study, we have documented

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**Fig 7.** Line graph shows mesenteric vascular resistance (MVR) as a function of infusion rate of angiotensin II (ANG II) in the presence and absence of infusions of prostaglandin I₂ (PGI₂) in normotensive, indomethacin-treated Wistar-Kyoto (WKY) rats treated from 4 weeks of age with captopril (100 mg/kg per day). See Fig 10 for summary of statistical analysis.

**Fig 8.** Line graph shows mesenteric vascular resistance (MVR) as a function of infusion rate of angiotensin II (ANG II) in the presence and absence of infusions of prostaglandin I₂ (PGI₂) in indomethacin-treated spontaneously hypertensive rats (SHR). See Fig 10 for summary of statistical analysis.

**Fig 9.** Line graph shows mesenteric vascular resistance (MVR) as a function of infusion rate of angiotensin II (ANG II) in the presence and absence of infusions of prostaglandin I₂ (PGI₂) in indomethacin-treated spontaneously hypertensive rats (SHR) treated from 4 weeks of age with captopril (100 mg/kg per day). See Fig 10 for summary of statistical analysis.
Repeatedly in chronic studies that the dosage regimen of captopril used in the current study completely and reliably prevents the development of hypertension in SHR.\(^2\)\(^3\) Most recently, we have confirmed this contention using round-the-clock telemetry measurements of arterial blood pressure in SHR for several months (manuscript in preparation). Therefore, our results indicate that in the SHR the Ang II/PGI\(_2\) interaction is defective and this defect is not an artifact of PGI\(_2\)-induced hypotension, is not induced by chronic hypertension, and is renal selective. Our results are entirely consistent with our previous work using intravenous infusions of PGI\(_2\) and Ang II\(^1\) and with the studies by Chatziantoniou and Arendshorst,\(^9\) who also observed that bolus intrarenal injections of PGI\(_2\) attenuated the renal vascular response to concomitant bolus intrarenal injections of Ang II in WKY rats but not in SHR.

In the present study, the systemic effects of PGI\(_2\) and Ang II were minimized by infusing these hormones in the aorta just above the origins of the mesenteric and renal arteries. However, some recirculation of both hormones was unavoidable. Regarding PGI\(_2\), the highest dose of PGI\(_2\) appeared to decrease arterial blood pressure in SHR that were chronically treated with captopril, although this affect did not achieve statistical significance. It is important to note, however, that regardless of the doses of Ang II and PGI\(_2\), the results were the same; ie, PGI\(_2\) attenuated the Ang II-induced renal vasoconstriction in WKY rats but not in SHR. This finding indicates that recirculation of either PGI\(_2\) or Ang II did not confound the results.

The data from our current studies can be viewed from several different perspectives. The graphical presentations in Figs 1 through 4 were designed to illustrate the point that PGI\(_2\) attenuates the renal vascular response to Ang II in WKY rats but not in SHR. Another informative perspective of the data is to overlay Fig 1 on Fig 3 and Fig 2 on Fig 4. This view of the data would demonstrate that in indomethacin-pretreated rats in the absence of exogenous PGI\(_2\), renal vascular responses to Ang II are similar in WKY rats versus SHR. However, in indomethacin-pretreated rats receiving infusions of exogenous PGI\(_2\), renal vascular responses to Ang II are greater in SHR versus WKY rats. This result applies whether or not animals are chronically treated with captopril. Thus it would appear that the enhanced renal response to Ang II that we and others have observed is abolished by indomethacin but reappears when PGI\(_2\) levels are restored by exogenous infusions of PGI\(_2\). This is further supporting evidence that the reason SHR have an increased renal responsiveness to Ang II is because of the inability of PGI\(_2\) to attenuate the renal response to Ang II.

Importantly, defective modulation of Ang II-induced vasoconstriction appears to be confined to the kidney. As shown in Figs 8 and 9, PGI\(_2\) effectively attenuated mesenteric vasoconstriction in SHR. This result is consistent with our recent observation of defective PGI\(_2\) modulation of Ang II-induced vasoconstriction in the kidney but not mesenteric after intravenous infusions of PGI\(_2\) and Ang II. As mentioned above, in a recent study we compared the effects of intravenous infusions of Ang II on regional hemodynamics in chronically captopril-treated SHR and WKY rats.\(^3\) Interestingly, in that study only the kidney demonstrated an enhanced responsiveness to Ang II. Thus, the renal-selective defect in the Ang II/PGI\(_2\) interaction observed in both the current study with intrarenal infusions and our previous study with intravenous infusions\(^1\) corresponds to the renal-selective enhancement of Ang II-induced vasoconstriction observed after intravenous infusions of Ang II.\(^3\)

Another issue deserving comment is the effect of chronic captopril treatment on vascular responses to Ang II. Chronic treatment with captopril significantly (captopril/Ang II interaction had a probability value of .0018 in the four-factor ANOVA) increased renal vascular responses to Ang II but did not significantly affect mesenteric vascular responses to Ang II. The interaction between captopril and Ang II in the kidney was not significantly dependent on rat strain (captopril/strain/Ang II interaction had a probability value of .2876 in the four-factor ANOVA). These results imply that regardless of rat strain, chronic blockade of the renin-angiotensin system upregulates receptor number and/or enhances postreceptor events in the renal but not mesenteric vasculature. This observation is consistent with our recent study demonstrating that the kidney vasculature is the primary physiological target for the renin-angiotensin system (manuscript submitted for publication). Thus, whenever the renin-angiotensin system is chronically inhibited, its primary physiological target, ie, the renal vasculature,
upregulates its responsiveness to Ang II to compensate for the reduced levels of Ang II.

In summary, the current study demonstrates that in the absence of PGI₂-induced hypotension and regardless of whether hypertension is allowed to develop, a renal-selective defect is observable in the SHR with steady-state infusions of Ang II and PGI₂. Exploration of the biochemical mechanism underlying this phenomenon may provide important clues to the genetic basis of hypertension in SHR and humans.

Acknowledgments

This work was supported by grants from the National Institutes of Health (HL-35909 and HL-14192), Bethesda, Md. Dr Curtis K. Kost, Jr, read and discussed this manuscript with the authors before submission, and we would like to acknowledge his very useful comments.

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Hypertension. 1994;23:329-336
doi: 10.1161/01.HYP.23.3.329

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