Role of Prostanoids in Renin-Dependent and Renin-Independent Hypertension

Lang Lin, Mahesh Mistry, Charles T. Stier Jr., and Alberto Nasjletti

We investigated the role of prostanoid-mediated pressor mechanisms in setting the level of blood pressure in renin-dependent and renin-independent models of hypertension in unanesthetized rats. Intravenous administration of a blocker of thromboxane A2/prostaglandin endoperoxide receptors, SQ29548 (2 mg/kg bolus injection plus 2 mg/kg/hr for 3 hours), reduced from 162±4 to 144±5 mm Hg (p<0.05) the blood pressure of rats with aortic coarctation-induced hypertension at 7-14 days after coarctation when plasma renin activity is greatly increased. In contrast, treatment with SQ29548 was without effect on the blood pressure of either normotensive or hypertensive rats (i.e., aortic coarctation-induced hypertension at 90-113 days after coarctation, deoxycorticosterone-salt-induced hypertension) having normal or depressed values of plasma renin activity. The blood pressure-lowering effect of SQ29548 in the early phase of aortic coarctation-induced hypertension was positively correlated with the prevailing plasma renin activity and could not be demonstrated in hypertensive rats pretreated with indomethacin. We attribute the hypotensive effect of SQ29548 to interference with pressor mechanisms that depend on activation of thromboxane A2/prostaglandin endoperoxide receptors and suggest that such prostanoid-mediated mechanisms are operational and contribute to an increase in blood pressure in angiotensin-dependent forms of hypertension. Also prostanoid-mediated vasodepressor mechanisms are operational in the early phase of aortic coarctation-induced hypertension since the blood pressure of rats pretreated with SQ29548 was increased by the subsequent administration of indomethacin. Accordingly, the blood pressure of rats with aortic coarctation-induced hypertension is influenced by the interplay of prostanoid-mediated pressor and vasodepressor mechanisms. (Hypertension 1991;17:517-525)

Inhibitors of cyclooxygenase were reported to lower the blood pressure of human subjects and rats with renin-dependent hypertension.1-4,6 Inasmuch as the cyclooxygenase inhibitors also caused reduction of plasma renin activity, the accompanying hypotensive effect was attributed to diminished expression of prostanoid-mediated mechanisms of renin secretion.1-4 However, the blood pressure-lowering effect of inhibitors of cyclooxygenase in renin-dependent models of hypertension also may be the consequence of decreased synthesis of thromboxane (Tx)A2 and prostaglandin (PG) endoperoxides, which are known to stimulate contraction of vascular smooth muscle via activation of common receptors.5 The demonstration that inhibitors of cyclooxygenase cause blood pressure to fall in forms of renin-dependent hypertension suggests contribution of prostanoid-mediated pressor mechanisms to the hypertension.6

Recent studies have linked TxA2 or the PG endoperoxides to the mechanisms of angiotensin-induced hypertension. For example, a blocker of TxA2/PG endoperoxide receptors was reported to lower the blood pressure of rats made hypertensive by chronic angiotensin II infusion combined with high salt intake,7 and both a blocker of TxA2/PG endoperoxides and an inhibitor of thromboxane synthase were shown to reduce the blood pressure of anesthetized rats made hypertensive by short-term infusion of angiotensin II.8 It is not known whether vasoconstrictor prostanoids also contribute to pressor mechanisms in angiotensin-independent models of hypertension.

The present study was undertaken to contrast the role of prostanoid-mediated pressor mechanisms in setting the level of blood pressure in models of angiotensin-dependent and angiotensin-independent hypertension. The experiments were conducted in rats made hypertensive by complete ligation of the aorta between the renal arteries, a model of hypertension that is angiotensin-dependent in...
the initial stage and angiotensin-independent in the late stage, and in rats with deoxycorticosterone (DOC)-salt–induced hypertension, a model of angiotensin-independent hypertension. We contrasted the hypertensive rats and their normotensive controls in terms of plasma renin activity, production of TxBa and 6-keto-PGF1α by vascular tissue ex vivo, renal excretion of TxBa and 6-keto-PGF1α and effects on blood pressure of treatment with either a blocker of TXA2/PG endoperoxide receptors, an inhibitor of thromboxane synthase, or an inhibitor of cyclooxygenase.

Methods

General Procedures

Studies were conducted on male Sprague-Dawley and Wistar-Kyoto (WKY) rats purchased from Charles River, Wilmington, Mass., and on male stroke-prone spontaneously hypertensive rats (SHRSP) bred in our institution from breeders obtained from the National Institutes of Health. The rats were housed in individual metabolism cages or in group cages and were kept in a temperature-controlled (24°C) and humidity-controlled (50%) room that was illuminated between 6:00 AM and 6:00 PM. All surgical interventions were performed under anesthesia with methoxyflurane (Pitmen-Moore, Inc., Washington Crossing, N.J.) to block TXA2/PG endoperoxide receptor effect of U46619, a synthetic agonist for the TXA2/PG endoperoxide receptor.7 SQ29548 (2 mg/kg bolus injection followed by an infusion at 2 mg/kg/hr for 3 hours) was given as a 2 mg/kg bolus injection followed by an infusion at 2 mg/kg/hr, at which dosage it was previously shown to greatly reduce the pressor and the renal vasoconstrictor effect of U46619, a synthetic agonist for the TXA2/PG endoperoxide receptor.7 Several complementary experiments were conducted in rats with aortic coarctation-induced hypertension at 7–14 days after surgery. In the first experiment, we studied the effect on blood pressure of L657,925 (9-p-chlorobenzyl-6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl, Merck-Frosst Canada, Inc., Pointe-Claire-Dorval, Quebec, Canada), another blocker of TXA2/PG endoperoxide receptors,13 given as a 2 mg/kg bolus injection followed by an infusion at 2 mg/kg/hr for 3 hours. In a second experiment, the effects of indomethacin (10 mg/kg) on blood pressure and plasma renin were studied in rats pretreated with SQ29548 (2 mg/kg bolus injection plus 2 mg/kg/hr infusion). In a third experiment, the effect of SQ29548 (2 mg/kg bolus injection plus 2 mg/kg/hr infusion) on blood pressure...
was studied in rats pretreated with indomethacin (10 mg/kg bolus injection). Finally, in rats with aortic coarctation–induced hypertension at 7–14 days and 90–113 days after coarctation, we examined the blood pressure response to an intravenous infusion of Sar'-Ala'–angiotensin II (10 μg/min for 30 minutes, Sigma), a blocker of angiotensin II receptors, to investigate the degree of angiotensin-dependency of the hypertension.

Protocols 3 and 4 were executed on Sprague-Dawley rats (180–220 g) with and without DOC-salt-induced hypertension. The left kidney was removed through a left flank incision. Commencing 1 day after uninephrectomy, rats in one group received weekly subcutaneous injections of DOC (25 mg/kg after uninephrectomy, rats in one group received weekly subcutaneous injections of DOC (25 mg/kg Percorten pivalate, CIBA) and drank deionized saline (0.15 M NaCl), whereas animals in the control group remained untreated and drank deionized water. All the rats were fed a standard chow, and systolic blood pressure was determined by tail sphygmography. The experiments were conducted 35–40 days after uninephrectomy. Protocol 3 was designed to compare rats with and without DOC-salt–induced hypertension in terms of urinary excretion of prostanoids and release of prostanoids by rings of aorta. First, urine was collected for 24 hours for measurement of TxB2 and 6-keto-PGF1α. Next, after thoracotomy, the descending aorta was excised for estimation of in vitro release of TxB2 and 6-keto-PGF1α. Protocol 4 was designed to investigate in rats with DOC-salt–induced hypertension the effect on blood pressure of treatment either with SQ29548 to block TXA2/PG endoperoxide receptors or with indomethacin to inhibit cyclooxygenase. The blood pressure of unanesthetized rats was monitored via a cannula in the carotid artery, before and for 3 hours after the onset of intravenous administration of SQ29548 (2 mg/kg bolus injection plus 2 mg/kg/hr infusion) or indomethacin (10 mg/kg).

Protocol 5 was executed in SHRSP and in WKY rats. Commencing at 7 weeks of age, all rats were fed Stroke-Prone Rodent Diet 39-288 (Zeigler Brothers Inc., Gardners, Pa.) and were given saline to drink. About 4 weeks later, the rats were instrumented with an arterial and a venous cannula, and after the rats had recovered from the anesthesia, blood pressure was recorded before and for 3 hours after the onset of intravenous administration of SQ29548 (2 mg/kg bolus injection plus 2 mg/kg/hr infusion); a blood sample (0.3 ml) for measurement of plasma renin was obtained before and 3 hours after commencing drug treatment.

Analytical Procedures

Plasma renin activity was measured, as described previously,14 by radioimmunoassay of the angiotensin I (Ang I) generated during incubation (2 hours, pH 6.5, 37°C) of the plasma specimen (25 μl) with pooled plasma from 48-hour nephrectomized rats (0.5 ml) in the presence of disodium ethylenediaminetetraacetate (5 mM), 2,3-dimercapto-1-propanol (5 mM), and phenylmethysulfonyl fluoride (1.5 mM). Renin activity is expressed as nanograms of Ang I generated per milliliter of plasma per hour of incubation. The radioimmunoassay of Ang I was performed using reagents purchased from New England Nuclear, Boston, Mass.

The concentration of TxB2 and 6-keto-PGF1α in urine was measured by enzyme immunoassay after the prostanoids were extracted according to a published method.15 Enzyme-linked immunoassay of prostanoids was performed as described by Pradelles et al16 using reagents purchased from Cayman Chemical Co., Ann Arbor, Mich. The urinary excretion of prostanoids was calculated as the product of their concentration in the urine and the 24-hour urine volume and was expressed as nanograms per 24 hours.

The release of TxB2 and 6-keto-PGF1α from aortic rings was estimated as described previously.7,15 Briefly, the aortic rings were placed in 20-ml flasks containing Krebs-Ringer solution (2.0 ml) and were incubated for 20 minutes at 37°C in an atmosphere of 95% O2–5% CO2 with 100 cycle/min agitation. The amount of prostanoid released into the medium was measured by enzyme immunoassay of unextracted samples; the results were expressed as picograms of TxB2 and nanograms of 6-keto-PGF1α released during the 20-minute incubation period per milligram of dry tissue.

To measure serum TxB2, blood was left to clot in a glass tube at 37°C for 1 hour; after centrifugation, the concentration of TxB2 in serum was determined by enzyme immunoassay of unextracted samples.7

Statistical Analysis

Results are expressed as the mean±SEM. Analysis of variance followed by Newman-Keuls a posteriori test was applied to the analysis of data on the effect of drugs on blood pressure and of comparisons among rats with aortic coarctation and sham-operated controls. Data on the effect of drugs on plasma renin were analyzed by Student's t test for paired observations. Data obtained in rats with DOC-salt–induced hypertension and in normotensive controls were compared by unpaired Student's t test. The null hypothesis was rejected when p<0.05.

Results

Vascular Prostanoid Release, Renal Prostanoid Excretion, and Plasma Renin in Aortic Coarctation–Induced Hypertension and Deoxycorticosterone–Salt Hypertension

Table 1 contrasts sham-operated rats and rats with aortic coarctation in terms of mean arterial blood pressure, plasma renin activity, release of prostanoids from aortic tissue in vitro, and urinary excretion of prostanoids. Relative to the data in sham-operated controls, rats with aortic coarctation feature, both at 7–14 and 90–113 days after coarctation, elevation of blood pressure and of net release of TxB2 and 6-keto-PGF1α from rings of thoracic aorta.
TABLE 1. Mean Arterial Blood Pressure, Plasma Renin Activity, Net Release of Thromboxane B₂ and 6-Keto-PGFlα From Rings of Aorta Incubated in Krebs-Ringer Buffer, and Urinary Excretion of Thromboxane B₂ and 6-Keto-Prostaglandin Flα in Sham-Operated Rats and in Rats With Aortic Coarctation-Induced Hypertension

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sham operation (n=11)</th>
<th>Early phase (7-14 days) (n=9)</th>
<th>Late phase (90-113 days) (n=7)</th>
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</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>108±4</td>
<td>162±4*</td>
<td>163±4*</td>
</tr>
<tr>
<td>Plasma renin (ng Ang I/ml/hr)</td>
<td>1.42±0.40</td>
<td>16.27±2.17*</td>
<td>1.04±0.12</td>
</tr>
<tr>
<td>Aortic TxB₂ release (pg/mg/20 min)</td>
<td>45.6±3.1</td>
<td>134.9±10.7*</td>
<td>341.7±48.7*</td>
</tr>
<tr>
<td>Aortic 6-keto-PGF₁α release (ng/mg/20 min)</td>
<td>6.7±0.9</td>
<td>11.0±1.5*</td>
<td>14.2±3.1*</td>
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<tr>
<td>TxB₂ excretion (ng/24 hr)</td>
<td>18.9±3.2</td>
<td>34.9±6.7*</td>
<td>25.4±8.8</td>
</tr>
<tr>
<td>6-keto-PGF₁α excretion (ng/24 hr)</td>
<td>16.5±1.9</td>
<td>24.5±1.2*</td>
<td>11.1±1.8</td>
</tr>
</tbody>
</table>

Values are the mean±SEM. n, number of rats. Ang I, angiotensin I; Tx, thromboxane; PG, prostaglandin.

*p<0.05 relative to sham-operated rats.

incubated in Krebs-Ringer buffer. Rats with aortic coarctation of 7-14 days' duration also exhibited augmentation of plasma renin activity and of urinary excretion of TxB₂ and 6-keto-PGF₁α. In contrast, rats with aortic coarctation of 90-113 days' duration had levels of plasma renin and of urinary excretion of TxB₂ and 6-keto-PGF₁α that did not differ significantly from the corresponding values in sham-operated rats.

Table 2 contrasts normotensive controls and rats with DOC-salt-induced hypertension of 5 weeks' duration in terms of plasma renin activity, release of prostanoids from aortic tissue in vitro and urinary excretion of prostanoids. Like rats with aortic coarctation-induced hypertension at 7-14 days after coarctation, DOC-salt hypertensive rats featured increased net release of TxB₂ and 6-keto-PGF₁α from rings of thoracic aorta incubated in Krebs-Ringer buffer and augmented urinary excretion of TxB₂ and 6-keto-PGF₁α. As expected, unlike rats with aortic coarctation-induced hypertension of 7-14 days' duration, DOC-salt hypertensive rats had depressed plasma renin activity.

Response of Blood Pressure to Blockade of Thromboxane A₂/Prostaglandin Endoperoxide Receptors and Inhibition of Prostanoid Synthesis in Hypertensive Rats

As illustrated in Figure 1, the blood pressure of sham-operated normotensive rats was not affected by the intravenous administration of either the TxA₂/PG endoperoxide receptor blocker SQ29548, the thromboxane synthase inhibitor UK38485, the cyclooxygenase inhibitor indomethacin, or drug vehicle only. Similarly, the plasma renin activity of sham-operated rats was not affected by treatment with either SQ29548 (1.57±0.69 ng Ang I/ml/hr before and 1.42±0.64 ng Ang I/ml/hr after treatment), indomethacin (1.43±0.37 ng Ang I/ml/hr before and 1.27±0.25 ng Ang I/ml/hr after treatment), or drug vehicle only (1.33±0.41 ng Ang I/ml/hr before and 1.56±0.65 ng Ang I/ml/hr after treatment).

The infusion of drug vehicle for 3 hours also was without effect on the blood pressure of rats with aortic coarctation-induced hypertension, both at 7-14 days after coarctation (172±4 mm Hg before and 174±5 mm Hg after treatment) and at 90-113 days after coarctation (173±5 mm Hg before and 174±3 mm Hg after treatment). As detailed below, the effect on blood pressure of treatment with either SQ29548, UK38485, or indomethacin during the early phase of aortic coarctation-induced hypertension, 7-14 days after coarctation, was different from the effect of treatment during the late phase of the hypertension, 90-113 days after coarctation.

In the early phase of aortic coarctation-induced hypertension, the administration of the TxA₂/PG endoperoxide receptor blocker SQ29548 caused a prompt and sustained reduction of blood pressure of

TABLE 2. Systolic Arterial Blood Pressure, Plasma Renin Activity, Net Release of Thromboxane B₂ and 6-Ketoprostaglandin Flα From Rings of Aorta Incubated in Krebs-Ringer Buffer, and Urinary Excretion of Thromboxane B₂ and 6-Ketoprostaglandin Flα in Six Control Normotensive Rats and in 10 Rats With Deoxycorticosterone-Salt-Induced Hypertension

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>DOC-salt hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>138±3</td>
<td>204±5*</td>
</tr>
<tr>
<td>Plasma renin (ng Ang I/ml/hr)</td>
<td>1.41±0.23</td>
<td>0.22±0.05*</td>
</tr>
<tr>
<td>Aortic TxB₂ release (pg/mg/20 min)</td>
<td>28.8±5.2</td>
<td>153.9±17.0*</td>
</tr>
<tr>
<td>Aortic 6-keto-PGF₁α release (ng/mg/20 min)</td>
<td>5.8±0.3</td>
<td>11.8±1.1*</td>
</tr>
<tr>
<td>TxB₂ excretion (ng/24 hr)</td>
<td>3.7±0.4</td>
<td>13.3±3.9*</td>
</tr>
<tr>
<td>6-keto-PGF₁α excretion (ng/24 hr)</td>
<td>15.3±1.1</td>
<td>44.8±11.5*</td>
</tr>
</tbody>
</table>

Values are the mean±SEM. DOC, deoxycorticosterone; Ang I, angiotensin I; Tx, thromboxane; PG, prostaglandin.

*p<0.05 relative to control.
about 20 mm Hg without any associated alteration of plasma renin activity (Figure 2). In the late phase of the hypertension, treatment with SQ29548 affected neither blood pressure nor plasma renin activity (Figure 2). Another blocker of TXA2/PG endoperoxide receptors, L657,925, also decreased the blood pressure of rats in the early phase of aortic coarctation-induced hypertension (from 190±8 to 176±8 mm Hg 3 hours after the onset of treatment, p<0.05, n=6). The hypotensive effect of SQ29548 in the early phase of aortic coarctation–induced hypertension was nearly abolished in rats pretreated with indomethacin 1 hour before the administration of the TXA2/PG endoperoxide receptor blocker. In such animals (n=9), the mean blood pressure was 174±7 mm Hg before indomethacin, 175±6 mm Hg 1 hour after indomethacin, and 172±7 mm Hg after superimposed treatment with SQ29548 for 2 additional hours. Treatment with SQ29548 also was without effect on the blood pressure and plasma renin activity of SHRSP and normotensive WKY rats (Figure 3), and on the blood pressure of rats with DOC-salt-induced hypertension (Figure 4). As illustrated in Figure 5, the effect of SQ29548 on the blood pressure

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**Figure 1.** Line graphs showing mean arterial pressure of sham-operated rats before and during treatment with drug vehicle only, indomethacin, UK38485, or SQ29548. Results are mean±SEM.

**Figure 2.** Line graphs showing effects of SQ29548 on mean arterial pressure (MAP) and plasma renin activity (PRA) of rats with aortic coarctation–induced hypertension at 7–14 days and 90–113 days after coarctation. Results are mean±SEM. *Indicates significant difference (p<0.05) between control and treatment values. Ang I, angiotensin I.

**Figure 3.** Line graphs showing mean arterial pressure (MAP) and plasma renin activity (PRA) of stroke-prone spontaneously hypertensive rats (SHRSP) and of Wistar-Kyoto (WKY) normotensive rats before and during treatment with SQ29548. Results are mean±SEM.

**Figure 4.** Line graphs showing mean arterial pressure of rats with deoxycorticosterone-salt–induced hypertension before and during treatment with drug vehicle only, indomethacin, or SQ29548. Results are mean±SEM. *Indicates significant difference (p<0.05) between control and treatment values.
of normotensive and hypertensive rats varied in relation to the prevailing plasma renin activity. When plasma renin activity was below 3.0 ng Ang I/ml/hr, SQ29548 had no consistent effect on blood pressure. In contrast, when plasma renin activity exceeded 3.0 ng Ang I/ml/hr, as in the early phase of aortic coarctation–induced hypertension, treatment with SQ29548 resulted in reductions of blood pressure that correlated positively with the prevailing plasma renin activity ($r=0.92$ for data in the early phase of aortic coarctation–induced hypertension).

As shown in Figure 6, treatment with the thromboxane synthase inhibitor UK38485 was without effect on blood pressure in the early phase of aortic coarctation–induced hypertension, but caused sustained elevation of blood pressure in the late phase of the hypertension. That the concentration of TxB$_2$ in the serum of rats treated with UK38485 was less than 1% of the serum TxB$_2$ concentration in untreated rats demonstrates the effectiveness of UK38485 to inhibit thromboxane synthase (Figure 6).

In the early phase of aortic coarctation–induced hypertension in rats, treatment with the cyclooxygenase inhibitor indomethacin caused after 2 hours a small and transient decrease of blood pressure accompanied by reduction of plasma renin activity (Figure 7). However, if the rats had been pretreated for 1 hour with the Tx$_A_2$/PG endoperoxide receptor blocker SQ29548, the superimposed treatment with indomethacin caused a prompt increase of blood pressure; this effect of indomethacin was transient, since blood pressure declined gradually over the next 2 hours accompanied by reduction of plasma renin activity (Figure 8). Treatment with indomethacin caused transient elevation of blood pressure during the late phase of aortic coarctation–induced hypertension in rats (Figure 7), and sustained elevation of blood pressure in rats with DOC-salt–induced hypertension (Figure 4).

In rats with aortic coarctation–induced hypertension, an intravenous infusion of the angiotensin II receptor blocker Sar$^1$-Ala$^8$-angiotensin II reduced mean blood pressure after 30 minutes by 60±1 mm Hg (from 180±1 to 120±1 mm Hg, $p<0.05$) at 7–14 days after coarctation ($n=5$), and by 16±3 mm Hg (from 173±3 to 157±4 mm Hg, $p<0.05$) at 90–113 days after coarctation ($n=5$), indicating greater dependency of the hypertension on angiotensin II–mediated mechanisms during the early phase than during the late phase. The administration of Sar$^1$-Ala$^8$-angiotensin II did not significantly affect the blood pressure of SHRSP (192±9 mm Hg before and 188±12 mm Hg after treatment, $n=6$).

**Discussion**

The present study documents association of hypertension and increased production of TxB$_2$ and 6-keto-PGF$_{1\alpha}$ by aortic rings in both the early and the late phase of aortic coarctation–induced hypertension and in DOC-salt–induced hypertension. Association of hypertension and augmentation of TxB$_2$ renal excretion and rates of production by renal or vascular structures has been demonstrated previously in several models of experimental hypertension in rats including SHR, 17,18 renal ablation hypertension, 19 two-kidney, one clip hypertension, 20,21 and angiotensin II–salt–induced hypertension. 7,22 Association of hypertension and increased production of 6-keto-PGF$_{1\alpha}$ by vascular tissue also was demonstrated previously in various models of experimental hypertension. 15,23,24 That etiologically dissimilar forms of hypertension feature augmented production of TxB$_2$ and 6-keto-PGF$_{1\alpha}$ by vascular tissue suggests that high blood pressure per se may be a determinant of the abnormality in prostanooid production.

The primary finding of the present study is that the blood pressure of rats in the early phase of aortic coarctation–induced hypertension is reduced by treatment with SQ29548 or L657,925, agents that block the receptors shared by TxA$_2$ and the PG endoperoxides. Because treatment with SQ29548 did not affect the blood pressure of either normotensive rats or of rats in the late phase of aortic coarctation–induced hypertension, SHRSP, or rats with DOC-salt–induced hypertension, the blood pressure–lowering effect of SQ29548 appears to be selective for...
the early phase of the hypertension produced by aortic coarctation. One can also infer from these observations that neither the prevailing status of blood pressure nor of aortic TXB$_2$ production are predictive of the effect of SQ29548 on blood pressure (e.g., blood pressure and aortic TXB$_2$ production were both increased in the early and the late phase of aortic coarctation–induced hypertension but only in the early phase of the hypertension was blood pressure decreased by treatment with SQ29548).

Based on the evidence detailed below, whether SQ29548 elicits reduction of blood pressure appears related to the activity of the renin-angiotensin system. First, in the early phase of aortic coarctation–induced hypertension, a stage of the hypertension that features increased plasma renin activity and is angiotensin dependent, the blood pressure reduction elicited by SQ29548 was positively correlated with the prevailing plasma renin activity. Second, SQ29548 was without effect on the blood pressure of rats having values of plasma renin activity ranging from depressed in DOC-salt-induced hypertension to marginally increased in SHRSP. Third, as previously reported, SQ29548 lowers the blood pressure of rats made hypertensive by a combination of angiotensin II infusion and high salt intake. Collectively, these observations suggest that short-term treatment with the TXA$_2$/PG endoperoxide receptor blocker SQ29548 reduces blood pressure selectively in forms of hypertension that are angiotensin dependent to a great extent. It remains to be investigated whether prolonged administration of SQ29548 elicits sustained lowering of blood pressure in the early phase of aortic coarctation–induced hypertension.

In the present study, the blood pressure–lowering effect of SQ29548 in the early phase of aortic coarctation–induced hypertension could not be demonstrated in rats pretreated with indomethacin, implying that the expression of this effect of the blocker of TXA$_2$/PG endoperoxide receptors necessitates a background with prostanoid synthesis. Such a conditioning influence is to be expected if the hypertensive effect of SQ29548 is indeed the result of blockade of the pressor actions of TXA$_2$ or the PG endoperoxides, rather than the consequence of some other action of the agent. In this regard, previous studies in nor-
motensive rats revealed that SQ29548 interferes with the pressor and renal vasoconstrictor effects of U46619, a synthetic agonist for the TxA2/PG endoperoxide receptor, but not with the acute pressor and renal vasoconstrictor effects of norepinephrine and angiotensin II. Furthermore, SQ29548 does not appear to impede the direct vascular actions of angiotensin II, since angiotensin II (1 μM)–induced isometric contractions of isolated rings of thoracic aorta from normal rats are nearly identical in the absence (0.80±0.09 g, n=11) and presence (0.81±0.08 g, n=5) of SQ29548 (1 μM) (L: Lin and A. Nasjletti, unpublished observations). Based on these considerations, the selective blood pressure–lowering effect of SQ29548 in the early phase of aortic coarctation–induced hypertension may be taken as the consequence of interference with pressor mechanisms that depend on activation of TxA2/PG endoperoxide receptors. A corollary of this conclusion is that such mechanisms are operational and contribute to increased blood pressure in this model of angiotensin-dependent hypertension. A priori, the selective expression of pressor mechanisms mediated by activation of TxA2/PG endoperoxide receptors in angiotensin-dependent hypertension may be the consequence of actions of angiotensin II resulting in either increased synthesis, reduced metabolism, or augmented vascular effects of the primary endogenous agonists for such receptors (i.e., TxA2 and the PG endoperoxides).

Contribution of TxA2 to the pathogenesis of hypertension is suggested by reports that treatment with inhibitors of thromboxane synthase lowers blood pressure or interferes with the development of hypertension in several models in rats. However, there are also reports that treatment with inhibitors of thromboxane synthase is without effect on the blood pressure of SHR and of rats with angiotensin II-salt–induced hypertension. In the present study, the blood pressure of rats in the early and late phase of aortic coarctation–induced hypertension was either unchanged or increased rather than decreased after treatment with the thromboxane synthase inhibitor UK38485. The unexpected pressor effect of UK38485 in the late phase of aortic coarctation–induced hypertension may have been mediated by angiotensin II, since it was reported recently that inhibitors of thromboxane synthase increase the plasma renin activity of rats. Our results argue against the participation of TxA2 in the mechanisms of aortic coarctation–induced hypertension. Yet, a role for TxA2 in the mechanisms of hypertension cannot be excluded totally because the functional consequence of diminished TxA2 synthesis due to thromboxane synthase inhibition may be obscured by an attendant increase of PG endoperoxides, the precursors of TxA2 and PGs, which can also cause vasoconstriction.

Recent studies have implicated the PG endoperoxides in the mediation of endothelium-dependent mechanisms of vasoconstriction in SHR and in the early phase of aortic coarctation–induced hypertension. That the blood pressure of rats in the early phase of aortic coarctation–induced hypertension falls during treatment with blockers of TxA2/PG endoperoxide receptors, but is not reduced by the administration of an inhibitor of thromboxane synthase, suggests contribution of PG endoperoxides, rather than of TxA2, to the implementation of pressor mechanisms in this model of angiotensin-dependent hypertension. The present study also confirms that treatment with an inhibitor of cyclooxygenase, indomethacin, decreases plasma renin activity in the early phase of aortic coarctation–induced hypertension, implying that prostanoid-mediated mechanisms of renin secretion are operational and also may contribute to increased blood pressure in this model.

The conclusion that prostanoid-mediated mechanisms of vasoconstriction and renin secretion contribute to the pathogenesis of hypertension does not detract from the established notion that prostanoids such as PGI2 and PGE2 subserve antihypertensive functions. Relative to this point, treatment with cyclooxygenase inhibitors was reported either to decrease, increase, or be without effect on blood pressure, a difference in effects that may be taken as indicative of variations in the relative contributions of prostanoid-mediated pressor and vasodilator mechanisms to the setting of the level of blood pressure under various experimental conditions. For example, in this and a previous study, indomethacin tended to lower the blood pressure of rats in the early phase of aortic coarctation–induced hypertension, which is attributable to interference with the expression of the prostanoid-mediated mechanisms of vasoconstriction and renin secretion that are operational in this model of hypertension. Conversely, during blockade of TxA2/PG endoperoxide receptors by SQ29548 in the early phase of aortic coarctation–induced hypertension, in the late phase of aortic coarctation–induced hypertension, and in DOC-salt–induced hypertension, the administration of indomethacin caused prompt elevation of blood pressure, which is attributable to the elimination of prostanoid-mediated vasodilator mechanisms. Collectively, these findings support the notion that the level of blood pressure is influenced by prostanoid-mediated pressor and vasodilator mechanisms in the early phase of aortic coarctation–induced hypertension and in the late phase of aortic coarctation–induced hypertension.

In summary, the present study documents that treatment with SQ29548, a blocker of TxA2/PG endoperoxide receptors, selectively decreases the blood pressure of rats with aortic coarctation–induced hypertension at 7–14 days after coarctation, an effect that is positively correlated with the prevailing plasma renin activity. We attribute the hypotensive effect of SQ29548 to interference with pressor mechanisms that depend on activation of TxA2/PG endoperoxide receptors and suggest that such prostanoid-mediated
mechanisms are operational and contribute to increased blood pressure in angiotensin-dependent forms of hypertension. Prostanoid-mediated vasodilator mechanisms also appear to be operational in the early phase of aortic coarctation–induced hypertension, since indomethacin caused blood pressure to increase in hypertensive rats pretreated with SQ29548. Accordingly, the level of blood pressure in rats with aortic coarctation–induced hypertension may be influenced by the interplay of prostanoid-mediated pressor and vasodilator mechanisms.

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