Thromboxane Synthesis and Blood Pressure in Spontaneously Hypertensive Rats

MABEL L. PURKERSON, KEVIN J. MARTIN, JESSE YATES, JOHN M. KISSANE, AND SAULO KLAHR

SUMMARY The present study examines effects of administration of OKY 046, an inhibitor of thromboxane synthesis, for 100 days on systemic blood pressure and renal function in spontaneously hypertensive rats and in normotensive control rats. Untreated spontaneously hypertensive rats had higher values for thromboxane excretion in the urine and higher values for blood pressure than did normotensive control rats. Administration of OKY 046 decreased systolic and mean arterial blood pressure and urinary excretion of thromboxane and protein in spontaneously hypertensive rats. Administration of OKY 046 decreased thromboxane excretion in the urine of normotensive control rats but had no effect on blood pressure or protein excretion. Renal function, as assessed by the clearances of inulin and p-aminohippuric acid, was greater in spontaneously hypertensive rats treated with OKY 046 than in those receiving vehicle alone. In normotensive control rats, OKY 046 administration did not affect renal function. These results suggest that increased renal synthesis of thromboxane may play a role in the pathogenesis of the elevated blood pressure of spontaneously hypertensive rats. (Hypertension 8: 1113-1120, 1986)

KEY WORDS • hypertension • thromboxane • renal function • renal pathology

MECHANISMS responsible for development and maintenance of hypertension in spontaneously hypertensive rats (SHR) are still incompletely understood, yet the kidney is known to play a primary role in the development of hypertension. In the developmental phase of hypertension, SHR retain sodium, and this may contribute to the development of hypertension. This enhanced sodium-retaining capacity in young SHR may be caused by an increase in renal sympathetic nerve activity. 

The kidney has a high capacity to synthesize prostaglandins and thromboxane A_2. However, the contribution of these compounds, particularly thromboxane, to the renal function and the pathogenesis of hypertension in SHR remains to be elucidated. Shibouta et al. also reported that in 6-week-old SHR indomethacin and pinane-thromboxane A_2, a thromboxane A_2 antagonist as well as a thromboxane A_2 synthetase inhibitor, resulted in natriuresis accompanied by an increase in p-aminohippuric acid (PAH) and inulin clearances. On the other hand, pinane-thromboxane did not alter renal function in either 6-week-old normotensive Wistar-Kyoto rats (WKY) or 18-week-old SHR. These studies suggest that increased synthesis of thromboxane, a powerful vasoconstrictor, may play a role in the hypertension that develops in SHR. In addition, Uderman et al. have shown an attenuation of the development of hypertension in SHR after administration of the thromboxane synthetase inhibitor 4′-(imidazole-1-yl)-acetophenone.

Ablation of more than 70% of renal mass in the rat results in hypertension, proteinuria, and glomerulosclerosis of the remnant kidney. We have shown recently that rats with a remnant kidney have increased excretion of thromboxane B_2, the stable metabolite of thromboxane A_2, in the urine as compared with normal rats. Furthermore, oral administration of OKY 1581, a specific inhibitor of thromboxane synthesis, for 4 to
5 weeks in rats with a remnant kidney increased renal blood flow and glomerular filtration rate, decreased protein and thromboxane B₂ excretion in the urine, lowered blood pressure, and reduced the values for the ratio of heart weight to body weight to figures comparable to those seen in normal rats.¹⁴

The studies just described suggest a role for thromboxane A₂ in the development of hypertension in these two experimental models. In the present study we used SHR that received normal saline alone or OKY 046, a specific inhibitor of thromboxane synthesis, dissolved in normal saline and compared the results obtained in these rats with those obtained in normotensive WKY treated or not treated with OKY 046. The results of this study indicate that administration of OKY 046 moderates the elevation in systemic blood pressure of SHR and improves their renal function.

Materials and Methods

All studies were performed in adult female SHR weighing 160 to 210 g and normotensive WKY weighing 250 to 310 g (Taconic Farms, Germantown, NY, USA). Studies were initiated in both groups of rats when the animals were 8 weeks old (initial weights were comparable in all groups). The weights reported were those obtained at the time of study, 100 days later.

Animals were fed a standard rat chow containing 22.8% protein (Purina Lab Chow, Ralston-Purina, St. Louis, MO, USA) and allowed tap water ad libitum. A group of six SHR received OKY 046 (Lot 57-10-1; kindly provided by Ono Pharmaceuticals, Osaka, Japan), 20 mg/kg body weight b.i.d. subcutaneously in 0.3 ml of saline. Five SHR received 0.3 ml of saline subcutaneously b.i.d. (the vehicle in which the OKY 046 was dissolved). In addition, 12 WKY were studied. Six received OKY 046, 20 mg/kg body weight b.i.d. subcutaneously, while six (controls) received saline vehicle subcutaneously, 0.3 ml b.i.d. At sequential 2-week intervals, measurements of systolic blood pressure in unanesthetized rats were performed using the tail plethysmography method. For this procedure, the rats were placed in a quiet, temperature-controlled environment. A tail cuff was placed as proximal as possible, and five consecutive blood pressure readings were recorded using a Model PE-300 Electro-Sphygmomanometer equipped with a sensitive piezoelectric transducer (Narco Bio-Systems, Houston, TX, USA) connected to a Model 1241 Soltec recorder (Sun Valley, CA, USA). The blood pressure values reported are the average of five determinations. At the end of 100 days of drug or vehicle administration, clearance studies were performed.

Clearance Studies

Renal function in these rats was determined in the awake state using standard clearance techniques.¹⁴ ¹⁵ After an overnight fast, rats were anesthetized with ether for insertion of cannulas into the femoral artery, tail vein, and bladder. The animals were then placed in Plexiglas holders, and 1½ to 2 hours was allowed for recovery from anesthesia and for urine flow to become stable. A priming dose of chemical inulin (Fisher, St. Louis, MO, USA) and chemical PAH (Merck Sharp & Dohme, West Point, PA, USA), was infused over a 3-minute period, followed by a sustaining infusion that contained sufficient inulin and PAH to maintain plasma levels. The sustaining solution was infused at 39 μl/min. After an equilibration period of 60 minutes, urine and blood specimens were collected for clearance periods. Urine for all clearance periods was collected in previously weighed tubes immersed in iced water (to preserve the excreted thromboxane B₂). Plasma and urine aliquots were obtained for each clearance period for determination of inulin, PAH, sodium, potassium, and blood urea nitrogen. A 200-μl urine sample was frozen and stored at —70°C for determination of thromboxane B₂.

Other Measurements

Upon completion of clearance studies, animals were anesthetized briefly with ether while cannulas were removed. Rats were returned to their cages, and 2 days later, while anesthetized with sodium pentobarbital (Nembutal, Abbott Laboratories, Chicago, IL, USA), 30 mg/kg body weight, the mean arterial blood pressure was measured. Rats were then perfused with half-strength Karnovsky’s fixative through the aortic cannula.¹⁶ After delivery of 10 to 12 ml of fixative to the vascular bed, the kidneys were excised, placed in fresh fixative, and prepared for light microscopy. Light microscopy to assess glomerular and small renal blood vessel morphology was performed on hematoxylin-eosin-stained sections of one kidney of each rat. After the rats were killed, the heart was excised and weighed. Body weight was also determined, and the ratio of heart weight (in milligrams) to body weight (100 g) was calculated.¹⁷

Determination of Urine Protein and Blood Pressure

Urine protein and mean arterial blood pressure were also measured in all groups of rats. Before the performance of clearance studies, animals were placed in metabolic cages and allowed regular chow and water intake while urine collections were made for 24 hours. Protein, sodium, and potassium content were determined. Two days after clearance collections were completed, the rats were anesthetized with sodium pentobarbital, 30 mg/kg body weight, given intraperitoneally and mean arterial blood pressure was measured through the right femoral artery with PE-50 tubing connected to a mercury manometer.

Chemical and Radioimmunoassay Determinations

Inulin in urine and plasma was determined using the microanthrone method.¹⁸ Sodium and potassium concentrations were determined using a flame photometer (Model 43; Instrumentation Laboratories, Lexington, MA, USA). The PAH content of blood and urine was determined by a modification of the method of Smith et al.¹⁹ Urine protein was quantitated using the method of Lowry et al.¹⁹ Urine aliquots for determination of thromboxane B₂ (the stable metabolite of thromboxane B₂) was determined using radioimmunoassay.
Aβ) by radioimmunoassay were handled as follows. To a known volume of urine, usually 100 μl, was added [3H]thromboxane B2, 750 counts per minute (New England Nuclear, Boston, MA, USA). The sample was acidified to pH 3 to 3.5 with 0.1 N HCl acid and passed through an octadecylsilica C18 column that had been activated with 1 ml of methanol and washed with 5 ml of water. The sample was then eluted with 1 ml of 15% ethanol in water followed by 1 ml of petroleum ether and 2 ml of methylformate. The methylformate fraction contained the thromboxane B2. The methylformate fraction was then taken to dryness under a stream of nitrogen. Next, 50 μl of radioimmunoassay buffer was added to the tube and vortexed, and an aliquot was removed (15 μl) for liquid scintillation counting. Recovery from the octadecylsilica columns was routinely 85 to 90%. The remainder of the sample was then used in the radioimmunoassay. Each sample was radioimmunoassayed in duplicate for thromboxane B2. The antiserum was obtained from rabbits immunized with thromboxane B2 coupled to keyhole limpet hemocyanin. The antiserum was diluted 1:300,000. The antiserum to thromboxane B2 had less than 0.1% cross-reactivity, with nine prostanoid metabolites tested including the dinor thromboxane B2.

Calculations and Statistical Analysis
Clearances were calculated using standard formulas. An unpaired t test was used when comparing data from control versus experimental rats.

Results
Figure 1 shows values for systolic blood pressure obtained every 2 weeks using the tail plethysmography method in awake WKY receiving vehicle or OKY 046. No significant differences in systemic blood pressure were seen at any time interval between the treated and untreated group of WKY (see Figure 1). Values for systolic blood pressure in SHR given vehicle or OKY 046 are depicted in Figure 2. Systolic blood pressure values were significantly higher in SHR than in WKY. In contrast to the results obtained in WKY (see Figure 1), the SHR that received OKY 046 had significantly lower systolic blood pressures than the untreated animals. The data for mean arterial blood pressure obtained under anesthesia after 100 days in treated or untreated WKY and SHR are shown in Figure 3. Administration of OKY 046 had no effect on mean arterial blood pressure in WKY but decreased significantly mean arterial blood pressure in SHR. However, values for mean arterial blood pressure in SHR treated with OKY 046 were still significantly higher than the values observed in WKY.

Table 1 shows the mean values for body weight, mean arterial blood pressure, ratio of heart weight to body weight, inulin and PAH clearances, 24-hour excretion of protein in the urine, and urinary excretion of thromboxane in five SHR receiving vehicle and six SHR that received OKY 046 for 100 days. Body weights were not significantly different between the two groups (control vs treated). On the other hand, there was a significant decrease in mean arterial blood pressure in the animals treated with OKY 046 as compared with control animals. There was also a significant decrease in the ratio of heart weight to body weight, indicating a sustained decrease in blood pressure in the animals treated with the inhibitor of thromboxane synthesis. There was a significant increase in both inulin and PAH clearances, indicating preserva-
### Table 1. Body Weight, Blood Pressure, Heart Weight to Body Weight Ratio, and Renal Function Studies in SHR

<table>
<thead>
<tr>
<th>Group</th>
<th>Body wt (g)</th>
<th>MAP (mm Hg)</th>
<th>Heart wt/body wt</th>
<th>C_{in} (ml/min/kg)</th>
<th>C_{PAH} (ml/min/kg)</th>
<th>24-hr protein excretion (mg/ml, GFR)</th>
<th>TBX excretion (pg/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 5)</td>
<td>196.6 ± 4.7</td>
<td>153.7 ± 2.7</td>
<td>487 ± 17</td>
<td>11.0 ± 0.27</td>
<td>34.4 ± 2.02</td>
<td>49.2 ± 5.9</td>
<td>1006 ± 148</td>
</tr>
<tr>
<td>Treated (n = 6)</td>
<td>182.5 ± 5.0</td>
<td>109.1 ± 8.7*</td>
<td>412 ± 13.8†</td>
<td>14.1 ± 1.05†</td>
<td>52.5 ± 2.85†</td>
<td>23.6 ± 5.0†</td>
<td>310 ± 70§</td>
</tr>
</tbody>
</table>

Values are means ± SEM in SHR given vehicle or OKY 046 for 100 days.

MAP = mean arterial pressure; C_{in} = inulin clearance; C_{PAH} = p-aminohippurate clearance; GFR = glomerular filtration rate; TBX = thromboxane B_2.

*<p < 0.001, †<p < 0.01, ‡<p < 0.02, $<p < 0.005, compared with values in controls.

The urinary protein excretion decreased significantly from 49.2 mg/ml glomerular filtration rate in the control group to 23.6 mg/ml glomerular filtration rate in the treated group. As expected, thromboxane excretion decreased by about 70% in the animals treated with the inhibitor of thromboxane synthesis.

Table 2 presents data for body weight, mean arterial blood pressure, ratio of heart weight to body weight, inulin and PAH clearances, as well as protein and thromboxane excretion in normotensive WKY. The weight of these rats was significantly greater than those obtained in SHR of the same age. Mean arterial blood pressure (see Figure 3) and the ratio of heart weight to body weight (Figure 4) were significantly lower in these rats than in SHR. However, no differences between control WKY given vehicle and those treated with OKY 046 were observed in any of these measurements. There were also no differences in inulin clearances, clearance of PAH, and excretion of protein between WKY receiving vehicle or OKY 046. Of interest was the finding that basal thromboxane excretion was substantially lower in WKY than in SHR given vehicle (Figure 5). In addition, administration of OKY 046 decreased urinary thromboxane excretion in WKY as well as in SHR (see Figure 5). Despite this decrease in thromboxane excretion in WKY, there was no effect on renal function or blood pressure, in contrast to the effect observed in SHR. However, it should be pointed out that the absolute decrease in thromboxane excretion induced by OKY 046 in SHR was significantly greater than that observed in WKY. In addition, the levels of thromboxane excretion before the administration of OKY 046 in WKY were comparable to the levels observed in SHR after the administration of the inhibitor of thromboxane synthesis.

The vascular alterations seen in the kidney of SHR have been described previously. In the present studies we found no morphological differences between WKY given saline vehicle alone and those receiving OKY 046. No histological abnormalities were seen in either group.

Vascular changes, characterized by cellular thickening of small arteries and arterioles, were observed in untreated SHR (Figure 6). These vascular changes were not seen in the SHR that received OKY 046. No fibrinoid necrosis was seen in glomeruli or in small arteries or arterioles in SHR receiving either vehicle or OKY 046. After “blinding” the slides, two observers could identify with 83% accuracy the differences in the morphology of small muscular arteries and arterioles in SHR treated with OKY 046 and those that received vehicle (no treatment).

![Figure 3. Average values for mean arterial blood pressure in WKY and SHR after 100 days of receiving either vehicle (C) or treatment with OKY 046 (Rx). No significant difference in mean arterial blood pressure was observed between treated and untreated WKY. In contrast, a significant decrease in mean arterial blood pressure was observed in SHR treated with OKY 046 when compared with the untreated group.](image-url)
### Table 2. Body Weight, Blood Pressure, Heart Weight to Body Weight Ratio, and Renal Function Studies in Normotensive WKY

<table>
<thead>
<tr>
<th>Group</th>
<th>Body wt (g)</th>
<th>MAP (mm Hg)</th>
<th>Heart wt/body wt</th>
<th>C_pe (ml/min/kg)</th>
<th>C_PAH (ml/min/kg)</th>
<th>24-hr protein excretion (mg/ml, GFR)</th>
<th>TBX excretion (pg/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 6)</td>
<td>277 ± 9.5</td>
<td>90.9 ± 1.9</td>
<td>344 ± 13.2</td>
<td>12.8 ± 0.8</td>
<td>40.9 ± 2.2</td>
<td>29.6 ± 6.0</td>
<td>530 ± 60.7</td>
</tr>
<tr>
<td>Treated (n = 6)</td>
<td>252 ± 7.4</td>
<td>90.4 ± 1.2</td>
<td>317 ± 10.6</td>
<td>12.5 ± 0.8</td>
<td>38.0 ± 4.5</td>
<td>23.1 ± 3.1</td>
<td>54.7 ± 9.8*</td>
</tr>
</tbody>
</table>

Values are means ± SEM in WKY given vehicle or OKY 046 for 100 days. See Table 1 for key to abbreviations.

*p < 0.001, compared with values in controls.

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**Figure 4.** Ratio of heart weight to body weight (BW) in WKY and SHR untreated (C) or treated with OKY 046 (Rx) for 100 days. Note that the ratio of heart weight to body weight was greater in SHR than in WKY. This presumably is due to higher levels of arterial blood pressure in SHR than in WKY. Treatment with OKY 046 did not significantly affect the ratio of heart weight to body weight in WKY, but administration of this drug significantly decreased this ratio in SHR. However, the ratio of heart weight to body weight was still significantly greater in treated SHR than in the WKY. This difference presumably reflects the fact that mean arterial blood pressures in treated SHR did not decrease to the levels seen in normotensive WKY.

**Figure 5.** Urinary excretion of thromboxane B₂, the stable metabolite of thromboxane A₂, in WKY and SHR receiving vehicle (C) or OKY 046 (Rx). Treatment with OKY 046 significantly decreased the urinary excretion of thromboxane in both WKY and SHR. Note also that the urinary excretion of thromboxane B₂ was significantly greater in untreated SHR than in untreated WKY. BW = body weight.

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**Discussion**

The results of the present experiments indicate that administration of an inhibitor of thromboxane synthesis to SHR results in a decrease in arterial blood pressure, a decrement in the ratio of heart weight to body weight, decreased urinary excretion of thromboxane B₂, and higher values for insulin clearance and the clearance of PAH (an indirect measure of renal plasma flow). In contrast, administration of this inhibitor of thromboxane synthesis did not alter blood pressure, the ratio of heart weight to body weight, or the levels of
renal function in WKY. Of interest is the fact that SHR excreted almost twice as much thromboxane B₂ in the urine as did WKY. It is also of interest to note that administration of OKY 046, an inhibitor of thromboxane synthesis, decreased significantly the excretion of this metabolite of thromboxane A₂ in both SHR and WKY. Whether the increased urinary excretion of thromboxane is related to a primary abnormality in renal thromboxane synthesis in SHR or represents a phenomenon secondary to the hypertension is not clear from the present studies. However, previous experiments using glomeruli isolated from SHR or WKY at 6 to 8 weeks of age have demonstrated increased synthesis of thromboxane B₂ by glomeruli isolated from SHR as compared with those isolated from WKY. Since at this age values of blood pressure tend to be similar in the two groups of rats, these studies would suggest that a primary abnormality in the renal synthesis of thromboxane may be present in SHR. If this is the case, vasoconstriction of the renal vascular tree, particularly at the level of the afferent arteriole, may occur²² and may modify the response of the kidney to increases in systemic blood pressure. Thus, changes in renal hemodynamics that occur physiologically as a consequence of increases in blood pressure and that in turn could modify the renal excretion of sodium may not occur in SHR. Consequently, it is possible that profound renal vasoconstriction caused by increased thromboxane synthesis contributes to the marked increase in systemic blood pressure observed in SHR. When PAH clearance data were expressed in grams of kidney weight, we found that these values averaged 5.09 ml/min/g kidney weight in WKY (n = 6) and 3.86 ml/min/g kidney weight in SHR (n = 5) not receiving OKY 046. These values increased to 5.73 ml/min/g kidney weight in SHR receiving OKY 046.

Whether or not other tissues besides the kidney are also capable of producing increased amounts of thromboxane A₂ in SHR as compared with the same tissues obtained from WKY remains to be established. The morphological data presented in this study tend to support the notion that increased synthesis of thromboxane by the kidney results in profound vasoconstriction of the afferent arteriole and that administration of OKY 046 decreases not only the urinary excretion of thromboxane but also the vasoconstriction of the afferent arteriole, resulting in an increased diameter of the lumen of such vessels. Increased dilatation of the afferent arteriole may result in increased renal plasma flow, as measured by clearance of PAH, in treated SHR as
compared with untreated SHR, and this increase in plasma flow may in turn increase the rate of glomerular filtration, as observed in the present studies. Therefore, the changes in renal function observed in SHR do not appear to be related to a lowering of blood pressure but to an effect of OKY 046 in reducing the synthesis of thromboxane within the kidney, thus decreasing afferent arteriolar vasoconstriction, leading to increased renal plasma flow and, as a consequence, increased glomerular filtration rate. It is of interest that in the present studies no evidence of glomerulosclerosis was noted on renal histology despite marked hypertension for a period of 3 months in the SHR. Hence, one would have to postulate that the increase in renal function observed in SHR treated with OKY 046 was related to functional effects of the drug rather than to morphological changes.

The results of the present studies support the conclusion of Shibouta et al.5,6 and Uderman et al.7 that thromboxane may be involved in the development of hypertension in SHR. However, it is possible that OKY 046 might possess antihypertensive actions completely independent of thromboxane synthesis inhibition, such as direct vasodilatation or sympatholytic activity. Another possibility is that the observed antihypertensive effect was mediated either by the shunting of prostaglandin endoperoxides into pathways of prostacyclin biosynthesis or by increased vascular sensitivity to prostacyclin in the absence of thromboxanes. Although the increased excretion of thromboxane A2 in the urine suggests that this thromboxane is of renal origin, other possibilities should be considered. If platelet activation is involved in renal malfunction in some stages of the development of hypertension in SHR, the increased capacity of the platelets of this strain to produce thromboxane A2 as compared with WKY may explain the differences in excretion in the urine; hence, the urinary excretion of thromboxane may be related to differences in the behavior of platelets at the level of the kidney in SHR as compared with WKY. However, even if this were the origin of the increased thromboxane in the urine, the functional data tend to indicate that the increase in blood flow and glomerular filtration rate must have been related to an increase in perfusion and vasodilatation of the afferent arteriole. Hence, thromboxane of renal origin or platelet origin, or both, may be acting on the afferent arteriole to produce vasoconstriction in SHR but not in WKY.

Grone et al.24 have reported that glomerular filtration and renal plasma flow are decreased in young (6–8 weeks) SHR. Inhibition of thromboxane synthesis was demonstrated using UK 38485, an inhibitor of thromboxane synthetase. When given intravenously this inhibitor significantly increased glomerular filtration rate and renal plasma flow after acute treatment of SHR but not of WKY. They also treated SHR for 5 to 6 weeks by oral administration of UK 38485 (110 mg/kg body weight per day), which was initiated when the rats were 3 to 4 weeks of age. They found no decrease in blood pressure and no increase in renal function in the SHR given this compound orally as compared with untreated rats. Thus, their results are different from ours. The studies, however, are not strictly comparable. We used a different inhibitor of thromboxane synthesis, and our measurements of renal function were performed in older rats after approximately 14 weeks of treatment as compared with only 6 weeks in the studies of Grone et al.24 On the other hand, we observed significant decreases in blood pressure in SHR treated with OKY 046 as compared with a lack of effect of a similar inhibitor in the studies of Grone et al.24 The explanation for the conflicting results in these two studies is not immediately apparent but may relate to differences in the duration of treatment and age at which treatment was initiated. Uderman et al.8 found that therapy with a derivative of imidazole, an inhibitor of thromboxane synthesis, resulted in a lesser rise in arterial pressure in young SHR. In addition, Uderman et al.25 reported that administration for 12 days of UK 38485, the same inhibitor of thromboxane synthesis used by Grone et al.,24 decreased arterial pressure in adult SHR.

In summary, the renal production of thromboxane is increased in SHR as compared with that in normotensive (WKY) controls. This increased production seems to occur before the elevation in blood pressure. We postulate that increased renal production of thromboxane may play a role in the pathogenesis of the hypertension seen in SHR. However, since SHR treated with OKY 046 still had higher blood pressure values than WKY, we suggest that other mechanisms besides increased renal synthesis of thromboxane are involved in the development of hypertension in SHR.

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