Thromboxane A₂ and Development of Genetic Hypertension in the Lyon Rat Strain

Jocelyne Geoffroy, Daniel Benzoni, Madeleine Vincent, and Jean Sassard

To determine whether the increased renal biosynthesis of thromboxane A₂ observed in young genetically hypertensive rats of the Lyon strain could be involved in the development of their hypertension, Lyon hypertensive female rats received either thromboxane synthetase inhibitors (Dazmegrel or OKY 046) or a thromboxane A₂ receptor antagonist (AH 23848) during their prehypertensive stage. Treatment from 5 to 9 weeks of age with Dazmegrel failed to reduce systolic blood pressure. When given from 3 to 9 weeks of age, Dazmegrel and OKY 046 induced a similar progressive and specific reduction (60%) in the urinary excretion of thromboxane B₂ that was associated with a transient decrease in blood pressure level with Dazmegrel and a longer lasting blood pressure-lowering effect with OKY 046. AH 23848, given according to the same schedule, normalized the blood pressure level. This effect persisted 1 week after the cessation of the treatment. Interestingly, active doses of thromboxane synthetase inhibitors or of thromboxane A₂ receptor blocker required a 3-week delay to exhibit their antihypertensive properties. It is concluded that 1) the elevated production of thromboxane A₂ observed in young Lyon hypertensive rats is likely to participate actively in their blood pressure regulation and 2) this effect may be independent of its direct vasoconstrictor properties. (Hypertension 1990;16:655–661)

Thromboxane (Tx) A₂ exhibits potent platelet aggregation and vasoconstrictor properties through binding to specific TxA₂/prostaglandin (PG) H₂ receptors, which belong to two types, the α platelet receptors and the τ vascular receptors. Because of its biological properties, TxA₂ may be involved in blood pressure regulation and participate in the pathophysiology of genetic hypertension. This latter hypothesis is supported by the fact that increased TxA₂ biosynthesis or concentrations are observed in isolated perfused kidneys and in glomeruli, as well as in urine and serum of spontaneously hypertensive rats (SHR) of the Japanese strain. In another model of genetic hypertension, the Lyon model, we described a higher TxA₂ renal production in young (5- and 9-week-old) but not in adult Lyon genetically hypertensive (LH) rats compared with their two control normotensive strains. Such an alteration in TxA₂ biosynthesis seems to be specific to genetic hypertension, as it is not found in models that are sodium-dependent such as Dahl and Sabra rats. The antihypertensive effect of chronic Tx synthetase inhibition in SHR led to controversial observations. Grone et al observed no change in systolic blood pressure (SBP) after long-term treatment with Dazmegrel, a Tx synthetase inhibitor, or with BM 13505, another TxA/PGH₂ receptor antagonist. BM 13505, another TxA₆/PGH₂ receptor antagonist, failed to reduce SBP in SHR rats. By contrast, others obtained a reduction in the blood pressure elevation or a delay in the development of hypertension by using different thromboxane synthetase inhibitors such as OKY 046, 4(1H-imidazol-1-yl) acetophenone, or CV 4151.

The present study was undertaken to determine whether the increased renal synthesis of TxA₂, which we described in young LH rats, could participate in the development of hypertension. This was assessed by studying the effects of long-term treatment with two different thromboxane synthetase inhibitors or with a TxA₂/PGH₂ receptor antagonist given during the prehypertensive stage.

Methods

Animals

Ninety-six LH and 24 genetically normotensive (LN) female rats were divided into groups of 12. The use of females instead of males has been preferred, as it
excludes the contamination of urines with prostaglandin-containing seminal fluid. The rats were housed under strictly controlled conditions of temperature (21±1°C), lighting (12-hour light/dark cycle, 8 AM–8 PM), and humidity (60±10%). They received a regular diet (UAR AO3 Entretien, UAR, Villemoisnon/Orge, France) and had free access to tap water.

Drugs

Two specific Tx synthetase inhibitors, Dazmegrel and OKY 046, and one TxA$_2$/PGH$_2$ receptor antagonist, AH 23848, were used. Dazmegrel ([UK 38485: 3-(1H-imidazol-1-yl-methyl)-2-methyl-1H-indol-1-propanoic acid], supplied by Pfizer Central Research, Sandwich, Kent, England, was suspended in arabic gum (10% weight/volume) and administered by gavage. In preliminary experiments, we used the dose of 100 mg/kg/day usually found in the literature. It was reduced to 75 mg/kg/day in the rats aged from 3 to 5 weeks because we observed toxic effects. OKY 046 ((E)-3-[p-(1H-imidazol-1-yl-methyl)phenyl]-2-propanoic acid) was obtained from Ono Pharmaceutical Company Limited, Osaka, Japan. According to Purkerson et al., it was dissolved in NaCl 0.9% and given at the dose of 20 mg/kg body wt twice daily by the subcutaneous route. AH 23848 ([1α(Z),2β,5α]-(-7-[5-[1,1'-bi-phenyl]-4-yl]-methoxy]-2-(4-morpholinyl)-3-oxo cyclo-pentyl)-4-heptenoic acid), supplied by Glaxo Group Research Limited, Greenford, Kent, England, was dissolved in sodium bicarbonate 8% (weight/volume). Preliminary experiments, using platelet aggregation as an index of TxA$_2$/PGH$_2$ receptor blockade, were designed to determine the dose to be used. They showed an inhibition of 65.7±4.5% (n=4), 83.9±0.6% (n=5), and 91.8±1.0% (n=3) 1 hour after a single oral dose of 1, 2, and 4 mg/kg, respectively. The dose of 2 mg/kg inhibited platelet aggregation by 86.3±3.7% (n=7) and 72.1±0.3% (n=7) at 12 and 24 hours, respectively, after a single oral administration. Therefore, the dose of 2 mg/kg twice daily was chosen. The slow onset of the antihypertensive action of AH 23848 observed in the present study and reported below led us to determine the kinetics of the vascular TxA$_2$/PGH$_2$ receptor blockade by AH 23848. For that purpose, 8-week-old female rats (five LN and five LH rats) were prepared with arterial and venous femoral catheters, which were tunneled subcutaneously and exteriorized between scapulae. One day later, the arterial catheter was connected to a blood pressure transducer (model P23ID, Statham, Cleveland, Ohio) coupled to a blood pressure analyzer (Gould processor amplifier, model 134615-52, Cleveland, Ohio). The venous catheter was used for bolus injections of a submaximal dose (5 µg/kg) of U46619 (Sigma Chemical Co., St. Louis), a TxA$_2$/PGH$_2$ receptor agonist, which were performed before and after an oral administration of 2 mg/kg AH 23848. In the two strains, basal SBP levels remained unchanged after AH 23848 administration. As shown in Figure 1, the pressor effect of U46619 recovered by 50% 3 hours after AH 23848 administration and returned to control levels 5 hours after.
under light ether anesthesia, blood was obtained from the jugular vein in one half of LH rats for platelet aggregation study and in the other half for the measurement of plasma creatinine.

**Methods**

SBP was recorded weekly immediately before the administration of drugs or vehicle by an indirect tail plethysmographic method (Narco Biosystems, Houston) in the prewarmed (37°C for about 10 minutes) unrestrained conscious rat. At least three readings were obtained by a blinded investigator and averaged for each animal and each time. The 24-hour urinary excretion of TxB2, 6-keto-PGF1α, and PGE2 was used as an index of the renal production of TXA2, prostacyclin (PGI2), and PGE2, respectively.17,18 It was determined using our previously described method.19

In this technique, urinary PGs and TxB2 were first extracted by ethyl acetate and then submitted, before specific radioimmunoassays, to a reversed phase, high-performance liquid chromatographic separation performed on a column packed with Nucleosil C18 (particle size, 10 μm) using a mobile phase made of water, acetonitrile, and acetic acid (79:21:0.1) at a flow rate of 2.3 ml/min. This step is of major importance as it allows a separation of 6-keto-PGF1α, TxB2, and PGE2 from the other primary PGs and also of 6-keto-PGF1α and TxB2 from their respective dinor derivatives, which are influenced by the systemic production of PGI2 and TXA2. Therefore, although our anti-6-keto-PGF1α and anti-TxB2 antibodies partly cross-reacted with the corresponding dinor derivatives (10.7% and 26.7%, respectively), any interference was avoided during the radioimmunoassays. The urinary excretion of Na+ and K+ was determined by flame photometry (IL meter). Urinary and plasma creatinine were measured according to Jaffe's colorimetric method. TxA2 receptor blockade was assessed by the inhibition of platelet aggregation.20

Starting with a citrated blood sample (5 ml), platelet aggregation study was performed using a dilution of platelet-rich plasma (PRP) (centrifugation 130g, 10 minutes) and platelet-poor plasma (PPP) (centrifugation 1,000g, 15 minutes) provided by the same rat. The test was realized in triplicate in disposable polystyrene cuvettes containing 0.5 ml PRP stirred at 1,100 rpm during 1 minute in the aggregometer. Platelet aggregation was induced by bovine thrombin (Hoffman Laroche, Basel, Switzerland) used at the concentration of 3 units/ml diluted in Tyrode's solution (pH 7.4).

**Results**

**Thromboxane Synthetase Inhibition**

When started at 5 weeks of age, long-term treatment with Dazmegrel did not influence SBP of LH rats (Figure 2) despite an inhibition of TxB2 urinary excretion of 34% (15.6±2.4 versus 9.7±1.1 ng/24 hr) and 54% (6.3±1.1 versus 2.9±1.1 ng/24 hr) after 1 and 4 weeks of treatment, respectively (Figure 3). Dazmegrel did not modify either 6-keto-PGF1α and PGE2 urinary excretion or diuresis, natriuresis, and kaliuresis (Table 1).

When started at 3 weeks of age, Dazmegrel and OKY 046, at the doses used, induced a similar inhibition of the TxB2 urinary excretion (Figure 3) without modifying that of 6-keto-PGF1α and PGE2 (Table 2). In both cases, the TX synthetase inhibition was progressive, as the degree of inhibition was 35%
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FIGURE 3. Bar graphs showing urinary excretion of thromboxane (Tx) B_2 in groups of 12 Lyon hypertensive (LH) rats during chronic Tx synthetase inhibition with Dazmegrel between 5 and 9 weeks of age (panel A) and with Dazmegrel or OKY 046 between 3 and 9 weeks of age (panel B). Arrows indicate start and end of treatments.

(17.2±1.5 versus 11.2±0.9 ng/24 hr) and 29% (18.0±1.3 versus 12.7±1.2 ng/24 hr) after 2 weeks and 62% (2.6±0.4 versus 1.0±0.3 ng/24 hr) and 57% (6.8±0.5 versus 2.9±0.2 ng/24 hr) after 6 weeks of treatment for Dazmegrel and OKY 046, respectively. Diuresis, natriuresis, kaliuresis, and creatinine clearance were not influenced by either Dazmegrel or OKY 046 (Table 2). As shown in Figure 2, Dazmegrel treatment attenuated transiently (at the ages of 6 and 7 weeks only) the rise of SBP, whereas OKY 046 resulted in a normalization of SBP in 6-, 7-, and 8-week-old LH rats. Despite continuing the treatment, the antihypertensive effect of OKY 046 declined at 9 weeks of age and disappeared immediately after its cessation.

**Thromboxane A_2 receptor blockade.** Six weeks of long-term treatment with AH 23848 induced a platelet aggregation inhibition of 64.7±3.9%. AH 23848 did not modify the urinary excretion of TxB_2 (6.0±0.7 versus 6.6±0.9 ng/24 hr), 6-keto-PGF_1α and PGE_2, or the renal function parameters (Table 2). As shown in Figure 4, AH 23848 exerted a delayed but pronounced antihypertensive effect that appeared after 3 weeks of treatment and resulted in a normalization of SBP in 6-, 7-, and 8-week-old LH rats, which lasted 1 week after the end of the treatment.

**Discussion**

The present work demonstrates that TxA_2 or PGH_2 are likely to participate in the development of hypertension in LH rats. However, it raises several questions because 1) two structurally related Tx synthetase inhibitors that induced a similar and progressive decrease in urinary TxB_2 exhibited different antihypertensive properties and 2) only a TxA_2/PGH_2 receptor antagonist was able to normalize, in a stable manner, the blood pressure of LH rats. Finally, it must be emphasized that the antihypertensive properties of Tx synthetase inhibitors or of TxA_2/PGH_2 receptor blockers required several weeks to become significant. Taken as a whole, these results suggest that the role of TxA_2 or of PGH_2 in genetic hypertension may be indirectly related to their vasoconstrictor effect.

The variable findings reported in the literature concerning the blood pressure effect of chronic Tx synthetase inhibition in SHR prompted us to explore the role of the elevated renal production of TxA_2 that we have observed in young LH female rats compared with LN controls. This was first investigated in young LH rats by studying the effects of two Tx synthetase inhibitors, Dazmegrel and OKY 046, which are imidazole derivatives of propanoic and propenoic acid, respectively. The extent of Tx synthetase inhibition and its possible consequences on the synthesis of other PGs were assessed by the measurement of the urinary excretion of TxB_2, 6-keto-PGF_1α and PGE_2, which are usually considered a valid index of the renal biosynthesis of TxA_2, PGI_2, and PGE_2, respectively. In addition, these urinary measurements track the evolution with age of PG synthesis in the same rats maintained in unstressed physiological conditions. The urinary excretion of TxB_2 and other PGs was determined using a specific method that, because of its chromatographic separation step, allows avoidance of any interference of the 2,3-dinor derivatives of TXB_2 and 6-keto-PGF_1α.

**TABLE 1. Effects of Thromboxane A_2 Synthetase Inhibition on Body Weight and Urinary Excretion of Prostaglandins and Electrolytes in Lyon Hypertensive Rats Treated From 5 to 9 Weeks of Age**

<table>
<thead>
<tr>
<th>Age (wk)</th>
<th>Rats</th>
<th>Body weight (g)</th>
<th>U6KV (ng/24 hr)</th>
<th>UE2V (ng/24 hr)</th>
<th>UNaV (μmol/24 hr)</th>
<th>UKV (μmol/24 hr)</th>
<th>Diuresis (ml/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>LHc</td>
<td>123±3.4</td>
<td>67.3±5.6</td>
<td>25.1±1.8</td>
<td>1,177±152</td>
<td>4,212±185</td>
<td>7.2±0.8</td>
</tr>
<tr>
<td></td>
<td>LH-Daz</td>
<td>121±2.4</td>
<td>65.1±5.5</td>
<td>25.9±2.3</td>
<td>1,086±137</td>
<td>4,062±192</td>
<td>6.9±0.4</td>
</tr>
<tr>
<td>9</td>
<td>LHc</td>
<td>189±4.0</td>
<td>33.5±2.1</td>
<td>20,14±151</td>
<td>5,147±256</td>
<td>11.6±0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LH-Daz</td>
<td>187±3.0</td>
<td>36.9±1.4</td>
<td>2,289±185</td>
<td>6,091±437</td>
<td>12.1±1.1</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM. U6KV, urinary excretion of 6-ketoprostaglandin F_1α; UE2V, urinary excretion of prostaglandin E_2; UNaV, urinary excretion of sodium; UKV, urinary excretion of potassium; LHc, Lyon hypertensive rats given vehicle; LH-Daz, Lyon hypertensive rats given Dazmegrel.
when considering the antihypertensive effects, the use of female LH rats, which exhibit an SBP level 20 mm Hg below that of age-matched males, did not facilitate our observations. The first attempt in which Dazmegrel treatment was started in 5-week-old LH rats was a failure, which can be explained by the time needed to reduce the activity of the renal Tx synthetase. Therefore, in a second experiment the treatment was started as early as possible (i.e., just after weaning), and we compared the effects of Dazmegrel with those of OKY 046. In these conditions, Dazmegrel transiently reduced the SBP elevation, and OKY 046 normalized it in 6-, 7-, and 8-week-old rats. The more pronounced and longer-lasting antihypertensive effects of OKY 046 compared with Dazmegrel cannot be accounted for by a difference in the Tx synthetase inhibition, as both drugs induced similar decreases in urinary TxB2. This finding raises the possibility of additional pharmacological properties of OKY 046. It is noteworthy that the SBP began to rise 1 week before the end of the treatment with OKY 046. Such an escape, also reported by Shibouta et al and Stier and Itzkovitz, suggests an upregulation of the number or of the sensitivity of TxA2/PGH2 receptors. In addition, no significant

### Table 2. Effects of Thromboxane A2 Synthetase Inhibition or Thromboxane A2/Prostaglandin H2 Receptor Blockade From 3 to 9 Weeks of Age on Body Weight and Urinary Excretion of Prostaglandins and Electrolytes of Lyon Hypertensive Rats

<table>
<thead>
<tr>
<th>Age (wk)</th>
<th>Rats</th>
<th>Body weight (g)</th>
<th>U6K.V (ng/24 hr)</th>
<th>UE2.V (ng/24 hr)</th>
<th>UNa.V (µmol/24 hr)</th>
<th>UK.V (µmol/24 hr)</th>
<th>Diuresis (ml/24 hr)</th>
<th>Creat. Clear. (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>LHc</td>
<td>105±2.2</td>
<td>63.1±5.2</td>
<td>22.0±2.1</td>
<td>770±62</td>
<td>2,036±46</td>
<td>7.0±1.6</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>LH-Daz</td>
<td>110±2.8</td>
<td>57.8±4.0</td>
<td>22.4±2.5</td>
<td>768±54</td>
<td>2,038±66</td>
<td>6.1±0.3</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>LHc</td>
<td>118±2.7</td>
<td>65.7±3.2</td>
<td>26.2±1.9</td>
<td>1,014±43</td>
<td>2,255±69</td>
<td>6.4±0.2</td>
<td>...</td>
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<tr>
<td></td>
<td>LH-OKY</td>
<td>118±1.9</td>
<td>69.4±3.2</td>
<td>27.3±2.2</td>
<td>1,037±55</td>
<td>2,179±63</td>
<td>6.0±0.3</td>
<td>...</td>
</tr>
<tr>
<td>9</td>
<td>LHc</td>
<td>121±1.2</td>
<td>31.8±2.3</td>
<td>34.1±5.0</td>
<td>1,372±73</td>
<td>2,886±107</td>
<td>13.8±0.7</td>
<td>51.3±2.9</td>
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<td></td>
<td>LH-Daz</td>
<td>123±2.6</td>
<td>30.9±3.7</td>
<td>34.7±3.7</td>
<td>1,355±79</td>
<td>2,688±136</td>
<td>12.0±0.6</td>
<td>50.2±2.6</td>
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<tr>
<td></td>
<td>LHc</td>
<td>213±3.4</td>
<td>34.1±1.5</td>
<td>31.9±1.6</td>
<td>1,568±48</td>
<td>3,178±128</td>
<td>12.0±0.7</td>
<td>77.0±2.7</td>
</tr>
<tr>
<td></td>
<td>LH-OKY</td>
<td>220±2.3</td>
<td>33.6±1.6</td>
<td>34.8±2.5</td>
<td>1,546±67</td>
<td>3,153±138</td>
<td>11.7±0.8</td>
<td>71.4±2.6</td>
</tr>
<tr>
<td></td>
<td>LHc</td>
<td>216±2.9</td>
<td>28.6±1.3</td>
<td>38.5±3.2</td>
<td>1,751±33</td>
<td>3,039±102</td>
<td>10.0±0.6</td>
<td>81.8±5.0</td>
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<tr>
<td></td>
<td>LH-AH</td>
<td>200±2.8</td>
<td>29.4±1.5</td>
<td>37.6±3.5</td>
<td>1,792±44</td>
<td>3,138±79</td>
<td>10.2±0.5</td>
<td>78.0±3.1</td>
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</table>

Values are mean±SEM. U6K.V, urinary excretion of 6-ketoprostaglandin F1α; UE2.V, urinary excretion of prostaglandin E2; UNa.V, urinary excretion of sodium; UK.V, urinary excretion of potassium; Creat. Clear., creatinine clearance; LHc, Lyon hypertensive rats given vehicle; LH-Daz, Lyon hypertensive rats given Dazmegrel; LH-OKY, Lyon hypertensive rats given OKY 046; LH-AH, Lyon hypertensive rats given AH 23848.
change could be observed in the glomerular filtration rate and in the urinary excretion of electrolytes.

In our last experiment, we turned to a\textsuperscript{2} \textit{Tx}A\textsubscript{2}/PGH\textsubscript{2} receptor antagonist to avoid any interference from the endoperoxides that act on the same receptor as does \textit{Tx}A\textsubscript{2}\textsuperscript{26} and accumulate during \textit{Tx} synthetase inhibition. Thus, we used AH 23848, which has been demonstrated to be without effect on the other prostaglandin receptors\textsuperscript{1} as well as on cyclooxygenase, \textit{Tx} synthetase or lipo-oxygenases\textsuperscript{1,27} and to be also devoid of platelet-stabilizing effects unrelated to the \textit{Tx}A\textsubscript{2} receptor blockade.\textsuperscript{28} Twelve hours after the end of the long-term treatment (2 mg/kg b.i.d.), AH 23848 inhibited the platelet aggregation by 65%. It did not alter the renal biosynthesis of \textit{Tx}A\textsubscript{2}, PGI\textsubscript{2}, or PGE\textsubscript{2}, a finding that confirms that this compound does not interfere with cyclooxygenase, PGI\textsubscript{2} synthetase, or isomerase.\textsuperscript{1} In our conditions, AH 23848 induced a stable normalization of SBP that, by contrast with OKY 046, persisted 1 week after the end of the treatment.

As a rule, the antihypertensive effect of \textit{Tx} synthetase inhibitors or of the \textit{Tx}A\textsubscript{2}/PGH\textsubscript{2} receptor blocker appeared after 3 weeks of treatment. Such a delay, which was also reported in SHR,\textsuperscript{7,8} could not be explained by the nature of the drugs used or by an accumulation of endoperoxides with \textit{Tx}A\textsubscript{2}-like actions, as the effects of these latter were also blocked by AH 23848. Therefore, one has to consider that \textit{Tx}A\textsubscript{2} may also act on SBP regulation by mechanisms differing from its direct and immediate vasocostrictor effect. This could explain the time-dissociated evolution between the inhibition of \textit{Tx} synthetase and the SBP decrease. Such an hypothesis is supported by our observation that an acute administration of AH 23848 did not reduce the SBP levels and that its inhibitory effects on the pressor action of a \textit{Tx}A\textsubscript{2}/PGH\textsubscript{2} agonist was much shorter lasting than that on platelet aggregation. It is also strengthened by the lack of antihypertensive action reported after acute administration of \textit{Tx} synthetase inhibitors in SHR\textsuperscript{8,9,15} as well as in patients with essential hypertension.\textsuperscript{25} These indirect mechanisms could involve an inhibition of the \textit{Tx}A\textsubscript{2} stimulatory effect on noradrenaline release\textsuperscript{29,30} or on the proliferation of vascular smooth muscle cells.\textsuperscript{31}

In conclusion, \textit{Tx} synthetase inhibitors and more markedly \textit{Tx}A\textsubscript{2}/PGH\textsubscript{2} receptor blockers are efficient antihypertensive drugs in genetically hypertensive rats of the Lyon strain when they are given immediately after weaning. The SBP effects of \textit{Tx}A\textsubscript{2} receptor blocker were found to be more potent and longer lasting than those of \textit{Tx} synthetase inhibitors. With both classes of compounds, a 3-week delay was required before the decrease in SBP occurred, a finding that points out that the control of blood pressure by \textit{Tx}A\textsubscript{2} may rely largely on indirect mechanisms. Finally, the present work demonstrates that \textit{Tx}A\textsubscript{2} is involved in the long-term blood pressure regulation of LH rats. Despite the absence of treated normotensive controls, it suggests that the increased renal and presumably extrarenal production of \textit{Tx}A\textsubscript{2} observed in young LH rats may be of importance in the pathogenesis of their hypertension.

Acknowledgments

We acknowledge the gift of Dazmegrel, OKY 046, and AH 23848 from Pfizer Central Research, Ono Pharmaceutical Company Limited, and Glaxo Group Research Limited, respectively. We thank Dr. S. Renaud and coworkers (INSERM, Unité 63, Lyon-Bron, France) for their help in the platelet aggregation studies. The help of B. Delmas in the study of the acute cardiovascular properties of AH 23848 was especially appreciated.

References


**KEY WORDS** • thromboxane A₂ • thromboxane synthetase • genetic hypertension • Lyon hypertensive rat strain
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