

# Thromboxane A<sub>2</sub> in Severe Hypertension and Stroke in Stroke-Prone Spontaneously Hypertensive Rats

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Thromboxane A<sub>2</sub> is a prostanoid having potent platelet aggregatory and vasoconstrictor properties. To determine a possible role for thromboxane A<sub>2</sub> in the development of severe hypertension and stroke, we chronically administered the selective thromboxane A<sub>2</sub> synthase inhibitor UK-38,485 (Dazmegrel) to stroke-prone spontaneously hypertensive rats (SHRSP). Serum thromboxane B<sub>2</sub> (the stable hydrolysis product of thromboxane A<sub>2</sub>) generation was significantly greater in incubates of whole blood from SHRSP than in those from normotensive control Wistar-Kyoto rats and was inhibited >89% by UK-38,485 administered in vivo. In 10 male SHRSP fed a Japanese-style rat chow and given 1% NaCl in drinking water to accelerate the occurrence of stroke, treatment with 100 mg/kg/day UK-38,485 by gavage starting at 8.6 weeks of age diminished systolic blood pressure elevation at 10 ( $205 \pm 2$  vs.  $220 \pm 4$  mm Hg,  $p < 0.01$ ) and 11 weeks of age ( $210 \pm 4$  vs.  $239 \pm 7$  mm Hg,  $p < 0.01$ ) compared with 10 untreated SHRSP. The ultimate establishment of severe hypertension was not prevented by UK-38,485. Stroke-related mortality was 70% in both UK-38,485-treated and control SHRSP at 14 weeks of age. Histologic examination revealed cerebrovascular lesions consistent with the occurrence of stroke in both control and UK-38,485-treated SHRSP. Our results support a possible role for thromboxane A<sub>2</sub> in the elevation of blood pressure in SHRSP but do not support a possible role for the prevention of stroke by thromboxane A<sub>2</sub> synthase inhibition in these rats. (*Stroke* 1988; 19:1145–1150)

Thromboxane (TX) A<sub>2</sub> is a metabolite of arachidonic acid having platelet aggregatory<sup>1</sup> and vasoconstrictor<sup>2</sup> properties and is generated in large amounts when platelets are stimulated to aggregate. Studies using a variety of TXA<sub>2</sub> synthase inhibitors suggest that TXA<sub>2</sub> contributes to blood pressure elevation in spontaneously hypertensive rats of the Okamoto-Aoki strain (SHR).<sup>3–5</sup> Increased concentrations of TXB<sub>2</sub> (the stable hydrolysis product of TXA<sub>2</sub>) have been observed in serum of incubated whole blood<sup>5–7</sup> and platelet-rich plasma<sup>6,8</sup> from SHR compared with normotensive Wistar-Kyoto rats (WKY), leading us to hypothe-

size that TXA<sub>2</sub> may play an important hypertension-ogenic role when vascular damage is present, such as in severe hypertension. SHR of the stroke-prone substrain (SHRSP)<sup>9</sup> develop severe hypertension and exhibit a high incidence (80%) of spontaneous cerebrovascular hemorrhage and/or infarction among males of >15 weeks of age; their average life span is 33–41 weeks. Pial arteries of SHRSP are generally thickened due to cellular hyperplasia and/or proliferation of adventitial cells and fibrinoid necrosis,<sup>9</sup> leading to microinfarction.<sup>10</sup> Parenchymal brain lesions are noted that are thought to be the result of vascular leakage.<sup>11,12</sup> These findings are prominent in the cerebrovasculature but are also observed in the heart, kidney, and other organs. It has been suggested that strokes in SHRSP are pathologically similar to those in humans.<sup>13</sup> Platelet survival has been found to be significantly reduced in SHRSP relative to stroke-resistant SHR and WKY.<sup>14</sup> Platelets of SHRSP injected into stroke-resistant SHR show normal survival, suggesting that shortened platelet survival is brought about by vascular abnormalities in SHRSP. Elevated sodium intake (by replacing normal drinking water with 1% NaCl solution) increases blood pressure and accelerates

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the onset of stroke in SHRSP.<sup>15</sup> SHRSP fed Japanese-style rat chow exhibit a higher incidence of stroke than those fed an American diet (88% vs. 30% by 9 months of age).<sup>16</sup> To test our hypothesis that TXA<sub>2</sub> is involved in the development of severe hypertension and stroke, SHRSP fed Japanese-style rat chow and given 1% NaCl solution to drink were chronically treated with the selective TXA<sub>2</sub> synthase inhibitor UK-38,485.<sup>17</sup>

### Materials and Methods

SHRSP derived from the Okamoto-Aoki strain of SHR and WKY were supplied by Dr. William Watson of the National Institutes of Health and were bred locally. Rats were weaned at 4–5 weeks of age and were fed a standard diet (Purina Lab Chow 5001, Ralston-Purina, St. Louis, Missouri) and allowed water ad libitum. We studied male SHRSP (generations F-56 and F-57) and WKY (generations F-41 and F-42) housed in individual cages.

Serum concentrations of TXB<sub>2</sub> were examined in eight 17-week-old SHRSP and six age-matched WKY maintained on standard chow and water to avoid possible changes in platelet counts due to acceleration of hypertension as such acceleration may occur with Japanese-style chow and saline. The effect of UK-38,485 was examined in a separate series of six 17-week-old SHRSP gavaged with 100 mg/kg/day UK-38,485 (divided between two doses) for 9 days and six 17-week-old SHRSP similarly gavaged with 10 ml/kg/day water. Twelve hours after the last dose, rats were anesthetized with 65 mg/kg i.p. sodium pentobarbital. Blood was removed from the aorta through a midline abdominal incision. Aliquots of whole blood (1 ml) were added to 12×75 mm borosilicate glass tubes (339-275, Curtin Matheson Scientific Inc., Wayne, New Jersey) and were incubated for 1 hour at 37° C.<sup>18</sup> After centrifugation at 3,000 rpm at 4° C for 10 minutes, serum was separated and stored at –28° C until assayed for TXB<sub>2</sub>. Concentrations of TXB<sub>2</sub> were determined in highly dilute serum samples without prior extraction using radioimmunoassay techniques as described.<sup>5</sup>

SHRSP used for blood pressure and survival studies were fed Japanese-style rat chow<sup>16</sup> (Ziegler Brothers, Gardiner, Pennsylvania) and were given 1% NaCl solution to drink ad libitum starting at 7.3 weeks of age. Body weight was measured daily. Systolic arterial blood pressure (SBP) was measured at weekly intervals in conscious rats using a Natsume KN 210 manometer and tachometer (Peninsula Laboratories, Inc., Belmont, California).<sup>19</sup> Rats were warmed at 37° C for 10 minutes and allowed to rest quietly in a Lucite chamber before tail-cuff plethysmography. Following a 5-minute stabilization period, an average of nine blood pressure and heart rate readings were obtained from each rat. At 8.6 weeks of age, chronic treatment with 100 mg/kg/day UK-38,485 (twice daily by gavage) was started in 10 SHRSP and was continued until death. Ten control SHRSP received an isovolemic gavage

of water (10 ml/kg/day, divided between two doses); littermates were used as controls to minimize the possible influence of differences between litters.

Survival was examined in four SHRSP given a higher dose (200 mg/kg/day) of UK-38,485 by gavage. Five control SHRSP received an isovolemic gavage of water (20 ml/kg/day, divided between two doses). The brains of SHRSP receiving high-dose UK-38,485 were also examined (see below).

The hearts, kidneys, and adrenal glands of rats that died were removed and weighed, and the brains were preserved in phosphate-buffered formaldehyde. Each brain was sliced transversely at five to seven levels and examined for gross abnormalities. The entire brain was then embedded in paraffin, and histologic sections (5–7 μm) from each were stained with hematoxylin and eosin and examined microscopically for lesions. Lesions were classified as infarct when neuronal necrosis or loss was accompanied by disintegration of the neuropil and infiltration by macrophages. Fibrinoid necrosis of vessels consisted of eosinophilic, hyaline material in thickened vessel walls. Rarefaction/edema consisted of a loosened, vacuolated, pale-staining neuropil of gray or white matter that did not show evidence of necrosis or dissolution. Hematoma was a solid mass of clotted blood, whereas petechial hemorrhages were much smaller foci of erythrocytes in the neuropil.

Data for multiple observations over time were analyzed for overall treatment effects using repeated-measures analysis of variance (SAS software package, Cary, North Carolina) and the Bonferroni method for comparison of treatment groups at different times. All other data were analyzed using unpaired *t* tests. Differences between means having a probability value of <0.05 were considered significant. Data are expressed as mean ± SEM.

### Results

Concentrations of TXB<sub>2</sub> were greater in incubates of whole blood from control SHRSP than from WKY (Figure 1, top). Inhibition of TXB<sub>2</sub> generation in whole blood from SHRSP treated with UK-38,485 was >89% (Figure 1, bottom).

Figure 2 shows SBP in control and UK-38,485-treated SHRSP. SBP was nearly identical in the two groups before and 5 days after commencing chronic treatment. However, SBP elevation was diminished at 10 (205 ± 2 vs. 220 ± 4 mm Hg, *p* < 0.01) and 11 weeks of age (210 ± 4 vs. 239 ± 7 mm Hg, *p* < 0.01) in SHRSP treated with UK-38,485. At 12–13 weeks of age, SBP became more variable and no longer differed between groups. In contrast, there was no difference in heart rate between the groups before or after treatment with UK-38,485 or water (data not shown). Body weight was not affected by chronic treatment with UK-38,485 and started to decline at 12–13 weeks of age in both groups. By 14 weeks of age, 70% of the rats in both groups had died (Figure 3); survival was comparable (the average age at

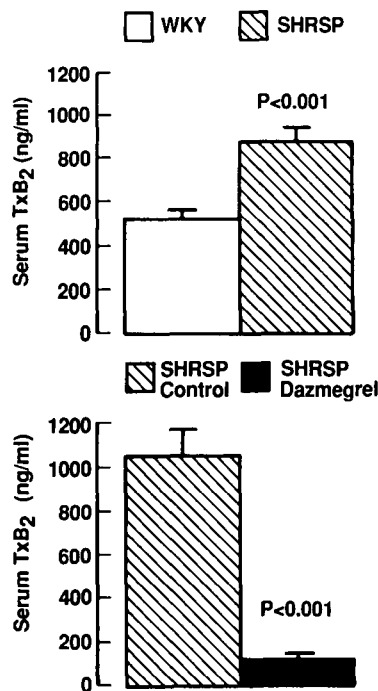


FIGURE 1. Serum thromboxane B<sub>2</sub> (TXB<sub>2</sub>) concentrations in incubates of whole blood from (top) eight stroke-prone spontaneously hypertensive rats (SHRSP) and six age-matched Wistar-Kyoto rats (WKY) and (bottom) six SHRSP treated with 100 mg/kg/day UK-38,485 (Dazmegrel) by gavage and six untreated control SHRSP. Values are mean  $\pm$  SEM.

death was  $14.4 \pm 0.5$  weeks in control SHRSP and  $14.3 \pm 0.4$  weeks in UK-38,485-treated SHRSP.

In four SHRSP high-dose UK-38,485 had no beneficial effect on survival. The age at death of high-dose UK-38,485-treated SHRSP ( $12.4 \pm 0.2$  weeks) was significantly less than that of control SHRSP ( $13.8 \pm 0.5$  weeks,  $p < 0.05$ ).

Body, heart, and adrenal gland weight at autopsy were not affected by chronic administration of UK-38,485 (Table 1). Total kidney weight tended to be less in SHRSP receiving UK-38,485; however, this difference was not significant. Lesions were observed on gross examination of the brains of rats from both groups. Histologic examination revealed hemorrhagic and anemic infarcts, rarefaction/edema, parenchymal hematomas, petechial hemorrhages, and hyalinosis, necrosis, and thrombosis of small vessels in both control and UK-38,485-treated SHRSP (Table 2). There were no significant differences in the incidence of cerebral lesions between the groups (Fisher's exact test). Most lesions were in the cerebral cortex. Some rats had multiple lesions, sometimes of different age or type.

Histologic analysis of the brains of high-dose UK-38,485-treated SHRSP also revealed evidence of cerebrovascular lesions (two had infarcts, two had petechial hemorrhages, and all exhibited rarefaction/edema).

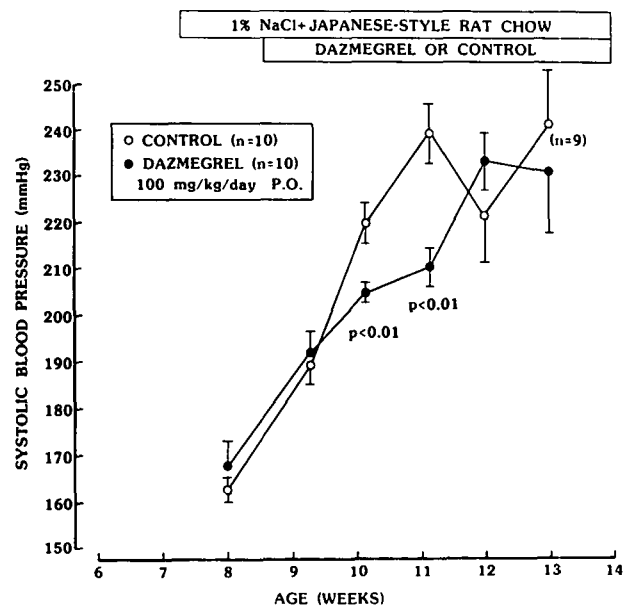


FIGURE 2. Systolic arterial blood pressure of stroke-prone spontaneously hypertensive rats maintained on 1% NaCl solution and Japanese-style rat chow. UK-38,485 (Dazmegrel) treatment (100 mg/kg/day by gavage) was started at 8.6 weeks of age. Control rats received isovolemic gavage of water (10 ml/kg/day). Values are mean  $\pm$  SEM.

## Discussion

SHRSP develop severe hypertension, vascular damage, and stroke, which are accelerated by dietary factors and elevated sodium chloride intake. Our study was conducted to evaluate the possible role of TXA<sub>2</sub> in the development of severe hypertension and stroke in SHRSP. As previously observed in SHR,<sup>5-7</sup> we found higher TXB<sub>2</sub> concentrations in serum of incubated whole blood from SHRSP than from WKY controls; formation of TXB<sub>2</sub> was inhibited >89% by in vivo administration of 100 mg/kg/day of the TXA<sub>2</sub> synthase inhibitor UK-38,485. We maintained our rats on a standard diet as under these conditions platelet counts in SHRSP are the same as in WKY<sup>14,20,21</sup> but otherwise are markedly reduced during accelerated hypertension<sup>20</sup>; such acceleration may occur when Japanese-style rat chow and saline are fed.

Chronic administration of UK-38,485 delayed the elevation of SBP in SHRSP but did not prevent the occurrence of severe hypertension. In previous studies, UK-38,485 (the TXA<sub>2</sub> synthase inhibitor we used) did not alter the elevation of SBP during chronic administration to SHR from 4 to 10 weeks of age.<sup>6</sup> In another study, mean arterial blood pressure was unchanged during the initial 12-hour period of UK-38,485 administration and SBP was not lowered until the fourth day of treatment with the TXA<sub>2</sub> synthase inhibitor in SHR with established hypertension.<sup>3</sup> Other TXA<sub>2</sub> synthase inhibitors have been found to delay blood pressure elevation in young SHR.<sup>4,5</sup> However, in 18-week-old

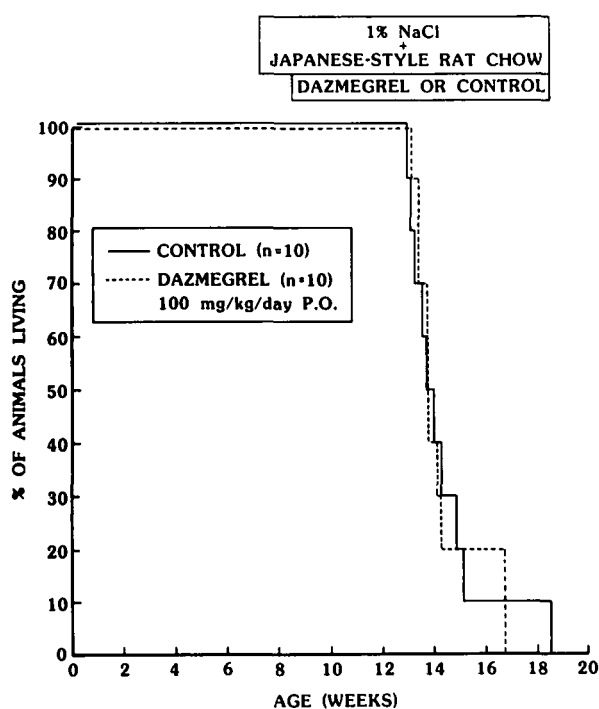


FIGURE 3. Survival of stroke-prone spontaneously hypertensive rats maintained on 1% NaCl solution and Japanese-style rat chow. UK-38,485 (Dazmegrel) treatment (100 mg/kg/day by gavage) was started at 8.6 weeks of age. Control rats received isovolemic gavage of water (10 ml/kg/day). Values are mean  $\pm$  SEM.

SHR with established hypertension, chronic administration of the TXA<sub>2</sub> synthase inhibitor CV-4151 had no effect on blood pressure.<sup>4</sup> In our studies of SHRSP developing severe hypertension, blood pressure was not lowered until after 5 days of UK-38,485 administration; this is consistent with other studies in which thromboxane synthase inhibitors fail to lower blood pressure acutely. Alternatively, the beneficial effect of chronic UK-38,485 treatment on blood pressure in SHRSP may derive from a delay in the progression of vascular injury, such as structural changes in the small arteries and thrombosis.

The mechanism by which UK-38,485 delays blood pressure elevation in SHRSP developing severe hypertension is not known. In addition to blocking the formation of TXA<sub>2</sub>, it is possible that the formation of vasodilatory/antiaggregatory prostanoids such as prostacyclin may be increased. Reorientation of endoperoxide metabolism has been demonstrated in vitro with several TXA<sub>2</sub> synthase inhibitors<sup>22,23</sup> and may occur in vivo under conditions of enhanced TXA<sub>2</sub> formation. Interestingly, chronic administration of the cyclooxygenase inhibitor indomethacin, which blocks the formation of prostacyclin in addition to TXA<sub>2</sub> and prostaglandin endoperoxides, did not inhibit the development of severe hypertension and slightly accelerated the development of proteinuria and stroke in SHRSP.<sup>24</sup> Another possibility is that UK-38,485 lowered blood pressure by altering water and electrolyte excretion or fluid intake. Although we did not measure these parameters, it is unlikely that significant alterations in fluid balance occurred as body weight was nearly identical in the two groups throughout the study. UK-38,485 also had no effect on heart rate in SHRSP, suggesting that diminished cardiac output secondary to reduced heart rate is not responsible for the fall in blood pressure. However, we cannot exclude shifts in body fluid compartment sizes or reductions in cardiac contractility (output) as having contributed to the lowered blood pressure in UK-38,485-treated SHRSP. Heart weight at autopsy was similar in control and UK-38,485-treated SHRSP and is consistent with the observation that blood pressure reduction was not sustained; severe hypertension ultimately developed in both groups.

Previous studies have suggested that TXA<sub>2</sub> synthase inhibitors may be of benefit in situations of acute thrombosis.<sup>23,25</sup> Our results indicate that chronic administration of the TXA<sub>2</sub> synthase inhibitor UK-38,485 offers no protection against the emergence of cerebrovascular lesions and stroke-related mortality in SHRSP. The extent of TXA<sub>2</sub> synthase inhibition (89%) we observed was substantial as its determination (made 12 hours after the last 50-mg/kg dose of UK-38,485) represents a mini-

TABLE 1. Body and Organ Weights of Stroke-Prone Spontaneously Hypertensive Rats at Autopsy

	Control (n = 10)	UK-38,485 (100 mg/kg/day) (n = 10)	p
Body (g)	160.3 $\pm$ 7.7	157.4 $\pm$ 8.5	>0.8
Heart			
Absolute (g)	0.88 $\pm$ 0.04	0.83 $\pm$ 0.06	>0.7
% of body wt	0.56 $\pm$ 0.03	0.52 $\pm$ 0.02	>0.2
Total kidney			
Absolute (g)	2.24 $\pm$ 0.13	1.91 $\pm$ 0.14	>0.05
% of body wt	1.42 $\pm$ 0.09	1.22 $\pm$ 0.07	>0.05
Total adrenal			
Absolute (mg)	50.9 $\pm$ 4.7	56.2 $\pm$ 4.8	>0.4
% of body wt	0.032 $\pm$ 0.003	0.036 $\pm$ 0.003	>0.3

Values are mean  $\pm$  SEM.

**TABLE 2. Lesions Observed on Microscopic Examination of Brains From Control and UK-38,485-Treated Stroke-Prone Spontaneously Hypertensive Rats**

Lesion	Control (n = 10)	UK-38,485 (100 mg/kg/day) (n = 10)
Acute or subacute infarct	6	4
Fibrinoid necrosis	4	4
Rarefaction/edema	8	7
Hematoma	1	1
Petechial hemorrhage	1	4
Hydrocephalus	3	2

Data are number of brains in which each lesion type was observed.

num value, with much greater inhibition occurring sooner after dosing. A higher dose of UK-38,485 (200 mg/kg/day) likewise failed to offer protection but rather, tended to promote stroke-related mortality in the few SHRSP studied. Based on our findings, a role for TXA<sub>2</sub> as a factor contributing to stroke cannot be excluded as inhibition of TXA<sub>2</sub> synthase may have increased levels of its parent compound, prostaglandin H<sub>2</sub>, which is known to cause contraction of vascular smooth muscle and platelet aggregation<sup>26</sup> by interacting with the TXA<sub>2</sub> receptor. Recently, we have found that chronic administration of the angiotensin I converting enzyme inhibitor enalapril prevents stroke-related mortality in salt-loaded SHRSP while only modestly affecting blood pressure.<sup>27</sup> In addition, the calcium channel blocking agent nitrendipine has also been found to prevent stroke in SHRSP without affecting blood pressure.<sup>28</sup> Thus, although TXA<sub>2</sub> may contribute to the blood pressure rise in SHRSP, other factors appear to be involved in the evolution of severe hypertension and stroke.

In summary, chronic administration of the TXA<sub>2</sub> synthase inhibitor UK-38,485 delayed but did not prevent the development of severe hypertension in SHRSP. UK-38,485 did not prevent stroke-related mortality or diminish the occurrence of brain lesions in SHRSP. Our results support a possible role for TXA<sub>2</sub> in the blood pressure elevation of SHRSP but not in the prevention of stroke by TXA<sub>2</sub> synthase inhibition.

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