Different Contributions of Endothelin-A and Endothelin-B Receptors in the Pathogenesis of Deoxycorticosterone Acetate–Salt–Induced Hypertension in Rats

Yasuo Matsumura, Norio Hashimoto, Shima Taira, Toshihiko Kuro, Rika Kitano, Mamoru Ohkita, Terry J. Opgenorth, Masanori Takaoka

Abstract—We investigated the involvement of actions mediated by endothelin-A (ET\textsubscript{A}) and endothelin-B (ET\textsubscript{B}) receptors in the pathogenesis of deoxycorticosterone acetate (DOCA)–salt–induced hypertension in rats. Two weeks after the start of DOCA-salt treatment, rats were given ABT-627 (10 \text{mg/kg}/d), a selective ET\textsubscript{A} receptor antagonist; A-192621 (30 \text{mg/kg}/d), a selective ET\textsubscript{B} receptor antagonist; or their vehicle for 2 weeks. Uninephrectomized rats without DOCA-salt treatment served as controls. Treatment with DOCA and salt for 2 weeks led to a mild but significant hypertension; in vehicle-treated DOCA-salt rats, systolic blood pressure increased markedly after 3 to 4 weeks. Daily administration of ABT-627 for 2 weeks almost abolished any further increases in blood pressure, whereas A-192621 did not affect the development of DOCA-salt–induced hypertension. When the degree of vascular hypertrophy of the aorta was histochemically evaluated at 4 weeks, there were significant increases in wall thickness, wall area, and wall-to-lumen ratio in vehicle-treated DOCA-salt rats compared with uninephrectomized control rats. The development of vascular hypertrophy was markedly suppressed by ABT-627. In contrast, treatment with A-192621 significantly exaggerated these vascular changes. In vehicle-treated DOCA-salt rats, renal blood flow and creatinine clearance decreased, and urinary excretion of protein, blood urea nitrogen, fractional excretion of sodium, and urinary N-acetyl-\beta-glucosaminidase activity increased. Such damage was overcome by treatment with ABT-627 but not with A-192621; indeed, the latter agent led to worsening of the renal dysfunction. Histopathologic examination of the kidney in vehicle-treated DOCA-salt rats revealed tubular dilatation and atrophy as well as thickening of small arteries. Such damage was reduced in animals given ABT-627, whereas more severe histopathologic changes were observed in A-192621–treated animals. These results strongly support the view that ET\textsubscript{A} receptor–mediated action plays an important role in the pathogenesis of DOCA-salt–induced hypertension. On the other hand, it seems likely that the ET\textsubscript{B} receptor–mediated action protects against vascular and renal injuries in this model of hypertension. A selective ET\textsubscript{A} receptor antagonist is likely to be useful for treatment of subjects with mineralocorticoid-dependent hypertension, whereas ET\textsubscript{B}-selective antagonism alone is detrimental to such cases. (Hypertension. 1999;33:759-765.)

Key Words: receptors, endothelin ■ hypertension, DOCA-salt ■ renal function ■ vascular hypertrophy

There is accumulating evidence indicating that endothelin-1 (ET-1) plays an important role in the development and/or maintenance of hypertension in animal models such as the deoxycorticosterone acetate (DOCA)–salt–induced hypertensive rat\textsuperscript{1–6} and Dahl salt-sensitive rat.\textsuperscript{7,8} This view is based on findings indicating that acute administration of an endothelin-A (ET\textsubscript{A})–selective receptor antagonist or nonselective ET\textsubscript{A}/ET\textsubscript{B} receptor antagonist to DOCA-salt rats produces a potent hypotensive effect and that long-term treatment with these agents efficiently suppresses the development of hypertension.\textsuperscript{2–4,7,8} Furthermore, it has been demonstrated that ET-1 content and ET-1 mRNA expression were elevated in vascular tissues of DOCA-salt hypertensive rats.\textsuperscript{4–6} Several studies have noted that hypertension-related renal damage in Dahl salt-sensitive rats and in rats with reduced renal mass was largely overcome by treatment with ET\textsubscript{A}-selective receptor antagonists.\textsuperscript{8,9} We noted the ameliorating effect of FR 139317, an ET\textsubscript{A}-selective receptor antagonist, on decreased renal function of DOCA-salt hypertensive rats.\textsuperscript{10} On the other hand, both ET\textsubscript{A}-selective and nonselective ET\textsubscript{A}/ET\textsubscript{B} receptor antagonists have been reported to prevent various cardiovascular diseases, such as acute ischemic renal failure\textsuperscript{11–13} and chronic heart failure,\textsuperscript{14,15} in animal models. Thus, it remains obscure as to whether blockade of the ET\textsubscript{A} receptor is beneficial for the treatment of subjects with cardiovascular diseases.
ABT-627 is the active enantiomer of the racemate A-127722, an orally active and highly potent ETₐ-selective receptor antagonist. The development of hypertension in DOCA-salt rats was significantly suppressed by long-term treatment with A-127722 (10 [mg/kg]/d). In addition, A-127722 has been reported to inhibit almost completely ETₐ receptors but is approximately 700-fold less potent for human ETₐ receptors. A-192621 effectively inhibits sarafotoxin S6c–induced contractions in isolated endothelium-denuded rabbit pulmonary artery (ETₐ, pA₂=3.2). The oral administration of A-192621 in a dose of 30 mg/kg has been reported to inhibit almost completely ETₐ receptor–mediated depressor and pressor responses. In the present work, to differentiate the roles of ETₐ and ETₐ receptors in the pathogenesis of cardiovascular diseases, we investigated the effects of chronic treatment with A-192621 on the development of hypertension, cardiovascular hypertrophy, and renal injury in DOCA-salt hypertensive rats and compared them with the effects seen with ABT-627.

Methods

Animals and Experimental Design

Male Sprague-Dawley rats (SLC, Inc, Hamamatsu, Japan) weighing 160 to 180 g were anesthetized with sodium pentobarbital (40 mg/kg IP), and the right kidney was removed via a right flank incision. After a 1-week recovery period, these rats were treated twice weekly with DOCA suspended in corn oil and administered subcutaneously (15 mg/kg), and 1% NaCl was added to their tap water for drinking. Control rats (n=10) were uninephrectomized but not given DOCA and salt. Two weeks after the start of DOCA-salt treatment, these rats were randomly divided into three groups and were given ABT-627 (10 [mg/kg]/d), A-192621 (30 [mg/kg]/d), or vehicle (50% distilled water). A-192621 was dissolved in 0.02N NaOH. Other chemicals were obtained from Nacalai Tesque and Kanto Chemical Industries. Drugs

ABT-627 and A-192621 were provided by Abbott Laboratories. ABT-627 was dissolved in a mixture of 10% ethanol, 40% propylene glycol, and 50% distilled water. A-192621 was dissolved in 0.02N NaOH. Other chemicals were obtained from Nacalai Tesque and Wako Pure Chemical Industries.

Statistical Analysis

Values are expressed as mean ±SEM. For statistical analysis, we used one-way ANOVA followed by Bonferroni’s multiple comparison test. For all comparisons, differences were considered significant at a value of P<0.05.

Results

Effects of Treatment with ABT-627 or A-192621 on BP of DOCA-Salt Hypertensive Rats

As shown in Figure 1, systolic BP was progressively elevated by treatment with DOCA and salt. After 2 weeks of treatment, systolic BP increased significantly compared with systolic BP in the uninephrectomized control group. Four weeks after the start of DOCA-salt treatment, the systolic BP of vehicle-
treated DOCA-salt rats was 285±6 mm Hg, whereas that of the uninephrectomized control group was 185±6 mm Hg. Daily oral administration of ABT-627 for 2 weeks markedly suppressed the development of hypertension induced by DOCA and salt. The observed increment during ABT-627 treatment for 2 weeks was only 4 mm Hg (from 136±3 mm Hg at 2 weeks to 140±3 mm Hg at 4 weeks). In contrast, A-192621 treatment did not affect the development of hypertension induced by DOCA and salt.

**Effects of Treatment with ABT-627 or A-192621 on Body, Heart, and Kidney Weights of DOCA-Salt Hypertensive Rats**

At 2 weeks of the experimental period, body weights of uninephrectomized control, vehicle-treated DOCA-salt, ABT-627–treated DOCA-salt, and A-192621–treated DOCA-salt rats were 285±6, 280±3, 284±4, and 288±4 g, respectively. At the end of the experimental period (at 4 weeks), the gain in body weight in vehicle-treated DOCA-salt rats was less than that in uninephrectomized control rats. As shown in Table 1, treatment with ABT-627 led to the recovery of body weight losses induced by DOCA and salt. Unexpectedly, 1 of the 6 rats treated with A-192621 died at 4 weeks (before urine collection). No brain hemorrhage was observed.

When heart, left ventricular, and left kidney weights were corrected for body weight, each organ weight-to-body weight ratio increased significantly in vehicle-treated DOCA-salt hypertensive rats. These increments were significantly suppressed by treatment with ABT-627 but not with A-192621 (Table 1).

**Effects of Treatment With ABT-627 or A-192621 on Blood and Urinary Parameters of DOCA-Salt Hypertensive Rats**

Table 2 summarizes renal functional parameters at the end of the experimental period. The levels of urinary excretion of protein, FENa, and urinary NAG activity in vehicle-treated DOCA-salt hypertensive rats were markedly elevated compared with findings in uninephrectomized control rats, although BUN in DOCA-salt rats did not increase significantly. On the other hand, significant decreases in creatinine clearance and renal blood flow were observed in vehicle-treated DOCA-salt hypertensive rats. These functional changes were markedly overcome by treatment with ABT-627. In contrast, A-192621 led to greater deterioration in functional parameters (except for FENa) than was seen in vehicle-treated DOCA-salt rats, achieving statistical significance in the levels of urinary excretion of protein and BUN.

**Effects of Treatment With ABT-627 or A-192621 on Histological Renal Damage in DOCA-Salt Hypertensive Rats**

Figure 2 shows typical examples in renal tissues of uninephrectomized control and DOCA-salt rats. Histological examination of the kidney in vehicle-treated DOCA-salt rats revealed relatively mild damage characterized by tubular

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### Table 1. Comparative Data on Body, Heart, and Kidney Weights in Uninephrectomized Control and DOCA-Salt Hypertensive Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>UN Controls</th>
<th>DOCA-Salt</th>
<th>DOCA-Salt + ABT-627</th>
<th>DOCA-Salt + A-192621</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>335±6</td>
<td>291±12*</td>
<td>333±6‡</td>
<td>223±10‡</td>
</tr>
<tr>
<td>HW/BW, g/kg</td>
<td>2.75±0.06</td>
<td>4.00±0.16*</td>
<td>3.30±0.12†</td>
<td>4.38±0.20*</td>
</tr>
<tr>
<td>LW/BW, g/kg</td>
<td>1.88±0.03</td>
<td>2.95±0.11*</td>
<td>2.41±0.07‡</td>
<td>3.25±0.16*</td>
</tr>
<tr>
<td>LKW/BW, g/kg</td>
<td>4.61±0.10</td>
<td>8.08±0.33*</td>
<td>7.03±0.37†</td>
<td>8.62±0.51*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. UN indicates uninephrectomized; BW, body weight; HW, heart weight; LW, left ventricular weight; LKW, left kidney weight.

*P<0.01 compared with UN group; †P<0.05, ‡P<0.01 compared with DOCA-salt group.

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### Table 2. Comparative Data on Blood and Urinary Parameters in Uninephrectomized Control and DOCA-Salt Hypertensive Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>UN Controls</th>
<th>DOCA-Salt</th>
<th>DOCA-Salt + ABT-627</th>
<th>DOCA-Salt + A-192621</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary excretion of protein, (mg/24 h)/100 g BW</td>
<td>4.28±0.31</td>
<td>73.84±0.04†</td>
<td>21.53±5.49§</td>
<td>136.44±28.68§</td>
</tr>
<tr>
<td>Creatinine clearance, (mL/min)/100 g BW</td>
<td>0.499±0.030</td>
<td>0.336±0.050*</td>
<td>0.555±0.041§</td>
<td>0.284±0.043†</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>26.5±1.6</td>
<td>29.4±3.6</td>
<td>22.0±1.2‡</td>
<td>44.5±2.6§</td>
</tr>
<tr>
<td>FENa %</td>
<td>0.38±0.05</td>
<td>18.26±4.00†</td>
<td>8.45±0.79†</td>
<td>18.06±0.31†</td>
</tr>
<tr>
<td>Urinary NAG activity, (U/24 h)/100 g BW</td>
<td>0.022±0.002</td>
<td>0.280±0.071†</td>
<td>0.182±0.008‡</td>
<td>0.335±0.051†</td>
</tr>
<tr>
<td>Renal blood flow, (mL/min)/g KW</td>
<td>5.05±0.60</td>
<td>2.26±0.32†</td>
<td>3.54±0.35</td>
<td>1.83±0.14†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Abbreviations are as in Table 1.

*P<0.05, †P<0.01 compared with UN group; ‡P<0.05; §P<0.01 compared with DOCA-salt group.
dilatation and atrophy as well as thickening of small arteries (Figure 2b). Treatment with ABT-627 reduced such damage (Figure 2c), whereas more severe histopathologic changes—such as fibrinoid-like necrosis in glomeruli, thickening of small arteries, tubular dilatation and atrophy, proteinaceous casts in tubuli, and interstitial cell infiltration—were observed in A-192621–treated animals (Figure 2d).

Effects of Treatment With ABT-627 or A-192621 on the Vascular Hypertrophy of DOCA-Salt Hypertensive Rats

Figure 3 shows examples of representative cross sections of the aorta obtained from 1 animal of each group. An increase in vascular medial thickness (wall thickness), a characteristic finding for hypertensive arterial hypertrophy, was clearly evident in vehicle-treated DOCA-salt rats. Treatment with ABT-627 but not with A-192621 markedly suppressed this vascular change induced by DOCA and salt. As summarized in Table 3, wall thickness, wall area, and wall-to-lumen ratio showed significant increases in vehicle-treated DOCA-salt rats compared with uninephrectomized control rats. ABT-627 decreased these parameters of vascular hypertrophy, and the observed values did not significantly differ from those for uninephrectomized control rats. In contrast, treatment with A-192621 significantly enhanced DOCA-salt–induced vascular changes.

Discussion

Physiological and pathophysiological responses to ET-1 in various tissues are mediated by interactions with ET_A and ET_B receptor subtypes. Both subtypes on smooth muscle cells mediate vasoconstriction, whereas the ET_B receptor subtype on endothelial cells mediates vasodilation, possibly through the release of endothelium-derived relaxing factor. ET-1 may contribute to the maintenance or regulation of BP through potent vasoconstrictive effects. However, the pathophysiological role of this peptide in the development and/or maintenance of hypertension has not been fully elucidated.

We have found that chronic treatment with FR 139317, an ET_A–selective tripeptide antagonist, suppressed the development of hypertension and cardiovascular hypertrophy in DOCA-salt hypertensive rats. Similar observations were obtained using the nonselective ET_A/ET_B receptor antagonist bosentan. In the present study, we used a newly developed ET_B–selective receptor antagonist, A-192621, and a highly potent ET_A–selective receptor antagonist, ABT-627, both of which are active when ingested orally. Our findings clearly indicated that daily administration of ABT-627 2 weeks after the start of DOCA-salt treatment markedly suppressed further increments in BP, accompanied by a significant decrease in cardiac and vascular wall hypertrophies. These results were qualitatively similar to those seen with FR 139317, although the antihypertensive effect of ABT-627 was indeed efficacious. In contrast, ET_B receptor blockade with A-192621 produced no significant effects on the development of hypertension induced by DOCA and salt. To our knowledge, this is the first report examining the long-term effect of an ET_B–selective receptor antagonist on the pathogenesis of an animal model of hypertension. Although heart weight and left
ventricular weight corrected by body weight were not significantly changed, the ET<sub>B</sub>-selective receptor antagonist enhanced DOCA-salt-induced arteriosclerotic changes. The latter finding suggests that ET<sub>B</sub> receptor–mediated action protects against vascular hypertrophy in this type of hypertension. This ET<sub>B</sub> receptor–mediated action may be attributed to endogenous endothelial nitric oxide generation, which inhibits mitogenesis and proliferation of vascular smooth muscle cells.<sup>25</sup> We recently noted that the aorta weight of DOCA-salt hypertensive rats was further increased by long-term treatment with the nitric oxide synthase inhibitor N<sub>G</sub>-nitro-L-arginine (Y.M. et al, unpublished data, 1998). Li et al<sup>26</sup> also noted the increased severity of conduit artery hypertrophy by treatment with N<sub>ω</sub>-nitro-L-arginine methyl ester in DOCA-salt hypertensive rats, although the agent reduced small artery hypertrophy through undetermined mechanisms. Regardless of mechanisms underlying ET<sub>B</sub> receptor–mediated actions, our findings mean that ET<sub>B</sub> receptor blockade is deleterious in this model of hypertension.

Effects of ABT-627 and A-192621 on renal function are of particular interest. Nephroprotective effects of chronic treatment with ETA-selective receptor antagonists have been noted using LU 135252 in stroke-prone spontaneously hypertensive rats<sup>27</sup> and using A-127722 in Dahl salt-sensitive rats.<sup>8</sup> In the present study, we also noted that treatment with ABT-627 markedly improved both glomerular and tubular functions in DOCA-salt hypertensive rats. On the other hand, Allcock et al<sup>18</sup> have recently observed that ETα receptor antagonism with A-127722 does not improve the decreased renal function in DOCA-salt hypertensive rats, although the agent attenuated the development and maintenance of hypertension in these rats. The reason for this discrepancy is unknown, but differences in experimental protocol (e.g., drug administration in drinking water in Allcock’s study versus by gavage twice daily in our study) may influence the efficacy of the drug. In contrast, functional damage of the kidney induced by DOCA and salt was accelerated by treatment with A-192621, as indicated by increases in urinary excretion of protein and BUN. In addition, these functional changes were accompanied by histopathologic changes in the kidney. Thus, ET<sub>A</sub> and ET<sub>B</sub> receptor antagonists revealed highly contrasting results against renal damage induced by DOCA and salt. Although further studies are required to clarify the mechanisms underlying the detrimental effect of ET<sub>B</sub> receptor blockade, endog-

### Table 3. Morphological Analysis of Aortas in Uninephrectomized Control and DOCA-Salt Hypertensive Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Wall Thickness, μm</th>
<th>Wall Area, mm&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Wall-to-Lumen Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>UN controls (n=5)</td>
<td>105 ± 4</td>
<td>0.542 ± 0.023</td>
<td>0.280 ± 0.008</td>
</tr>
<tr>
<td>DOCA-salt (n=5)</td>
<td>128 ± 4†</td>
<td>0.670 ± 0.013*</td>
<td>0.364 ± 0.022†</td>
</tr>
<tr>
<td>DOCA-salt + ABT-627 (n=5)</td>
<td>110 ± 3‡</td>
<td>0.563 ± 0.029‡</td>
<td>0.296 ± 0.009‡</td>
</tr>
<tr>
<td>DOCA-salt + A-192621 (n=5)</td>
<td>149 ± 5†‡</td>
<td>0.774 ± 0.031†‡</td>
<td>0.440 ± 0.017†‡</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. UN indicates uninephrectomized.

*P<0.05, †P<0.01 compared with UN group; ‡P<0.05, compared with DOCA-salt group.
enous ET-1/ET\textsubscript{A} receptor systems seem to function as a nephroprotective factor in DOCA-salt–induced hypertension.

Long-term treatment with A-192621 to uninephrectomized control animals produced no changes in renal functional parameters. ABT-627 also had no significant effect in uninephrectomized animals. We noted that renal vasoconstrictive effects induced by an intravenous bolus injection of BQ-788, a selective ET\textsubscript{A} receptor antagonist\textsuperscript{28}, were markedly enhanced in DOCA-salt hypertensive rats.\textsuperscript{29} On the other hand, we found that acute administration of FR 139317 to DOCA-salt hypertensive rats had a potent hypotensive effect and natriuretic effect (when renal perfusion pressure was protected from FR 139317–induced hypotension with an aortic clamp), although the agent had no significant effects on hemodynamic and excretory responses in normotensive animals.\textsuperscript{10} Taken together, it seems likely that endogenous endothelin does not play an important role in the regulation of renal function under normal conditions, in contrast to the case of DOCA-salt–induced hypertension, in which vascular and renal endothelin production is enhanced.\textsuperscript{4–6,30}

In the present study, systolic BP was monitored once a week and about 6 hours after drug administration (drugs were given twice daily every 12 hours). Thus, we did not observe BP changes that might occur immediately after drug administration. We recently noted that the hypertensive effects induced by an intravenous bolus injection of BQ-788 in DOCA-salt hypertensive rats were greater than those in uninephrectomized control normotensive animals (increase of 10 to 20 mm Hg in DOCA-salt rats versus one of 5 to 10 mm Hg in sham rats), although the increased level recovered at about 30 minutes after BQ-788 administration.\textsuperscript{29} Similar findings were observed using Ro 46–8443, the nonpeptide selective ET\textsubscript{B} receptor antagonist.\textsuperscript{31} In separate experiments, intravenous administration of A-192621 (3 mg/kg) to DOCA-salt hypertensive rats produced increases of 10 to 15 mm Hg in BP and decreases of about 60% in renal blood flow, changes that were greater than those observed in uninephrectomized control normotensive animals (increase of 5 to 10 mm Hg in BP and decreases of about 40% in renal blood flow) (Y.M. et al, unpublished data, 1998). Taken together, the possibility cannot be ruled out that transient changes in BP and renal hemodynamics induced by A-192621 administration are related to its deleterious effect on vascular hypertrophy and renal damage.

It is unclear whether the ameliorating effects of ABT-627 on the above vascular and renal changes result from its antihipertensive action. Recent studies indicated that the ET-1/ET\textsubscript{A} receptor system may be an important mediator in the pathogenesis of posts ischemic acute renal failure, based on findings that ET-1 mRNA expression is markedly enhanced in the posts ischemic kidney\textsuperscript{32} and that a selective ET\textsubscript{A} receptor antagonist prevents posts ischemic renal damage, such as decreases in renal blood flow and glomerular filtration rate, and tubular dysfunction.\textsuperscript{11,12} Further investigations are required to clarify whether the ABT-627–induced improvement in vascular hypertrophy and renal damage in DOCA-salt hypertension is independent of its antihypertensive activity.

In conclusion, selective ET\textsubscript{A} receptor blockade efficiently overcame the development of hypertension, vascular hypertrophy, and renal injury in DOCA-salt hypertensive rats, whereas selective ET\textsubscript{B} receptor blockade led to a deterioration in DOCA-salt–induced pathologies. Our working hypothesis is that ET\textsubscript{A} receptor–mediated actions are causal factors and ET\textsubscript{B} receptor–mediated actions are protective factors in the pathogenesis of DOCA-salt–induced hypertension. A selective ET\textsubscript{A} receptor antagonist should prove effective for treating subjects with mineralocorticoid-dependent hypertension.

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