Early-Onset But Not Late-Onset Endothelin-A–Receptor Blockade Can Modulate Hypertension, Cerebral Edema, and Proteinuria in Stroke-Prone Hypertensive Rats

Erwin L.A. Blezer, Klaas Nicolay, Roel Goldschmeding, Gerard H. Jansen, Hein A. Koomans, Ton J. Rabelink, Jaap A. Joles

Abstract—The ability of endothelin receptor blockade to prevent and to treat established cerebral and renal injury was explored in salt-loaded stroke-prone spontaneously hypertensive rats (SHRSP) with the endothelin receptor subtype-A antagonist A127722. SHRSP were subjected to 1% NaCl intake. The start of treatment with A127722 (35 and 70 mg · kg\(^{-1} \cdot \text{d}^{-1}\), respectively) was either synchronized with salt loading or initiated after the first observation of cerebral edema with T\(_2\)-weighted magnetic resonance imaging. In untreated control animals median survival was 54 days (range, 32 to 80 days) after the start of salt loading. Early-onset A127722 treatment increased median survival to 233 days (range, 92 to 407 days; \(P<0.05\) versus controls) with 35 mg/kg and to 124 days (range, 97 to 169 days; \(P<0.05\) versus control) with 70 mg/kg. The development of cerebral edema was prevented, and systolic blood pressure and proteinuria were dose-dependently reduced. However, all rats in the 70-mg/kg treatment group developed hemorrhages in the basal ganglia shortly before death. Late-onset A127722 treatment failed to affect survival, systolic blood pressure, or proteinuria. Nevertheless, cerebral edema was reduced but not as well as in early-onset treatment. Development of hypertension, cerebral edema, and proteinuria was prevented in SHRSP when A127722 treatment was initiated at the start of salt-loading. However, A127722 treatment did not prolong survival in SHRSP with cerebral edema. This suggests that in SHRSP the endothelin A receptor participates actively in the development of increased blood pressure and initiation of organ damage but participates minimally in established malignant hypertension and progression of target-organ damage. (Hypertension. 1999;33:137-144.)

Key Words: edema, cerebral \(\bigtriangledown\) rats, inbred strains \(\bigtriangledown\) magnetic resonance imaging \(\bigtriangledown\) endothelin receptors, endothelin \(\bigtriangledown\) proteinuria

Recently, endothelin (ET) receptor blockers have been advanced as possible antihypertensive drugs.\(^1\) It has been suggested that ET blockers may be particularly beneficial in modulating target-organ damage because of their antiproliferative actions.\(^2\) The predominant ET receptor expressed in vascular smooth muscle cells is the ET\(_A\) subtype that is mainly responsible for the vasoconstrictor\(^3\) and mitogenic\(^4\) effects of ET-1. ET receptor blockade has proven to be effective in ameliorating the development of hypertension and renal damage in chronic rat models, including renal failure,\(^5\) nitric oxide synthase inhibition,\(^6\) deoxycorticosterone acetate–salt treatment,\(^7\) deoxycorticosterone acetate—salt–treated spontaneously hypertensive rat (SHR),\(^8\) and in stroke-prone SHR (SHRSP) with or without salt treatment,\(^9\) but therapeutic effects on manifest target-organ damage, such as cerebral edema and renal injury, have not yet been reported.

To explore the role of ET-1 in severe hypertension and related target-organ damage, we used the salt-loaded SHRSP,\(^10\) a model in which we found consecutive development of hypertension, proteinuria, and cerebral edema\(^11\) and in which ET-1 levels are increased.\(^12\) Administration of a peptide ETA blocker was previously found to retard or prevent the development of hypertension or renal injury in the salt-loaded SHRSP model for 6 to 10 weeks after the initiation of treatment\(^9,13,14\); however, no studies are available on either long-term prevention or possible remission of manifest hypertensive lesions in this model.

\(T_2\)-weighted magnetic resonance imaging (T\(_2\)W-MRI) can be used to detect the initial appearance and to follow quantitatively the progression of cerebral edema in the salt-loaded SHRSP model.\(^11\) Recently, we found that angiotensin-converting enzyme (ACE) inhibition was able to reduce manifest cerebral edema and proteinuria and to prolong markedly survival in rats with proven cerebral and renal damage,\(^15\) suggesting an important role for angiotensin in sustaining target-organ damage in this model. In the present

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study we examined whether ET-1 plays a similar role and hence is an interesting target for therapeutic strategies. Oral administration of the potent and highly specific nonpeptide ET₄ receptor antagonist A127722,¹⁶ which has a proven antihypertensive effect,¹⁷,¹⁸ was synchronized either with the start of salt-loading, i.e., before the development of injury, or with the initial detection of cerebral edema to explore whether this antagonist is able to prevent and induce regression of established cerebral and renal damage.

Methods

Animals

Male SHRSP (n=28), age 6 weeks, were obtained from IFFA Credo, France. They had free access to a standard rat chow (RMH-TM rat chow; protein 22.2%; fat 4.8%; potassium 0.85%; sodium 0.40%; Hope-Farms) and were allowed water ad libitum. The protocol was approved by the Utrecht University Committee for study in experimental animals.

Protocol

Baseline measurements were made in all rats at 7 weeks of age. Subsequently, at the age of 8 weeks, all rats were switched to a high salt intake by adding 1% NaCl to the drinking water (170 mmol/L) to accelerate the appearance of cerebral edema.¹⁰ The rats were observed for overt neurological symptoms and underwent weekly blood pressure measurement and 24-hour urine collection.

Rats were continuously subjected to high salt intake, randomized into 5 groups, and treated orally via the drinking water with the potent and specific nonpeptide ET₄ receptor antagonist A127722.¹⁶ Group 1 (n=6) served as a control; in group 2 and group 3 (n=7 each), early-onset treatment with A127722 (35 and 70 mg · kg⁻¹ · d⁻¹, respectively, called A35 early and A70 early) was started together with the start of salt loading (day 0); in group 4 and group 5 (n=4 each) late-onset treatment with A127722 (called A35 late and A70 late, respectively) was started after the first observation of a focus of cerebral edema with T₂W-MRI (day 0₉ₐ₈). This dosage was just above the levels that achieved maximal inhibition of an ET-1–induced pressor response (0.3 nmol/kg) in conscious rats (namely, 10 and 30 mg/kg)¹⁹ and above a dose that attenuated but did not eliminate renal injury in Dahl salt-sensitive rats.²⁰ We presumed that these dosages would completely block the action of endogenously generated ET-1, the plasma concentration of which is much lower (8 pmol/L)²¹ in salt-loaded SHRSP, and that it would not block the ETB receptors.

Blood Pressure and Proteinuria

Systolic blood pressure (SBP) was measured with tail-cuff plethysmography (ITTC) weekly in the conscious rats.¹⁰ In all groups, 24-hour urine was collected weekly until proteinuria exceeded 40 mg/d. In group 1, urine collection was continued weekly until the end of the experiment. In groups 2 through 5, urine was collected weekly until 70 days after the start of A127722 treatment and thereafter every 14 days. Urinary protein was determined with the Bradford method.

T₂W-MRI

After inducing anesthesia with 1% halothane in N₂O/O₂ (70/30), rats were intubated and mechanically ventilated during the MRI session with the same mixture. Expiratory CO₂ was monitored and the body temperature maintained at 37°C using a heated water pad. The animals were fixed in a stereotaxic holder to prevent movement and positioned in a 4.7-T SIS Co 200-400 NMR-spectrometer. A 120-mm Helmholz coil was used for transmission and signal reception. After a sagittal scout image, coronal multislice spin-echo T₂W-MRI, covering the whole brain (25 slices of 1 mm; echo time/repetition time, 60/3000; matrix, 128×128; field of view, 40×40 mm; 2 transitions) was performed. The amount of cerebral edema was determined using methods described previously.¹¹

Histology

Directly after the last MRI session, the anesthetized animals were thoracotomized, and a cannula was inserted into the left ventricle for perfusion. A washout with isotonic heparinized (270 IU/kg) saline was performed (2 to 3 minutes), which was immediately followed by perfusion fixation with 4% formaldehyde in 0.1 mmol/L phosphate buffer at a pressure equal to two thirds of the last measured SBP. Brain and kidney were collected and stored in formaldehyde. Organs from rats that had died spontaneously were also collected. Staining of brains was performed with hematoxylin/eosin (HE) and Alcian Blue. Staining for Fe was performed according to Perls. Staining of kidneys was performed with periodic acid–Schiff reagent.

Glomerular damage was assessed in 100 glomeruli. Glomeruli received a score of 0 to 2, depending on the degree of injury present. A score of 0 denoted a normal or marginally affected glomerulus. Moderate glomerular damage (score of 1) was defined as partial collapse and mesangial sclerosis, involving up to 75% of the tuft (with or without adhesion to or thickening of Bowman’s capsule). Severe glomerular injury (score of 2) was characterized by total or subtotal collapse of the glomerular tuft, global sclerosis, or severe acute lesions with fibrinoid change. Total damage was calculated by summing the ratios of glomeruli in each category and multiplying by the category score.

Statistics

Two-way ANOVA for repeated measurements, followed by a pair-wise multiple comparison procedure (Student-Newman-Keuls method), was used to evaluate those time points with complete survival, the maximal level reached after initiation of treatment, and the last collected data point (terminal value). In A35 early and A70 early groups 1 rat each died during the anesthesia required for MRI measurement. These 2 rats were not included in the repeated-measures analysis. Data are presented as mean±SEM. Survival was evaluated with Kruskal-Wallis 1-way ANOVA for rank sums and is presented as median values and ranges. P<0.05 was considered statistically significant.

Results

Early-Onset Treatment

Survival

Comparison of survival shows the effectiveness of A127722 treatment (Figure 1a). Control animals had a median survival of 54 days (Table), whereas the A35 early and A70 early groups had a significantly prolonged survival of 233 days (P<0.05 versus control) and 124 days (P<0.05 versus control), respectively.

T₂W-MRI

As a result of salt loading the control animals developed cerebral edema at a median of 43 days (range, 25 to 59 days). The percentage of hyperintense pixels at this time point was 4.89±0.80%. As described previously,¹¹ cerebral vasogenic edema normally appeared in the cerebral cortex or the basal ganglia from which it spread (Figure 2a). The percentage of hyperintense pixels was increased 4-fold at the last collected data point (terminal level; Table). Although the development
of cerebral edema was completely prevented with both levels of ETA receptor blockade (Figure 2b and 2c), the percentage of hyperintense pixels increased slightly in the A35early and A70early groups (P < 0.05), although both were significantly lower than in control animals (P < 0.05; Table). This 1% to 3% increase in hyperintense pixels was the result of increased ventricle size in both groups (Figure 2b and 2c). In the A70early group, all animals developed hypointense spots in the basal ganglia (Figure 2c). Such hypointense spots invariably indicate hemorrhage, as was confirmed histologically (see below). This hemorrhage increased rapidly in size, and these rats’ conditions deteriorated and they died within 5 weeks after the first appearance of hemorrhage (median, 29 days; range, 4 to 35 days).

**SBP and Proteinuria**

SBP increased in control animals, from 198 ± 7 mm Hg by nearly 100 mm Hg (Figure 1b; Table). The development of hypertension was dose-dependently delayed or even halted by ETA receptor blockade (Figure 1b). In the A35early group, SBP became significantly lower than in the control group at day 21. However, by day 100 SBP reached a maximal level of 267 ± 2 mm Hg, a level similar to terminal values in the control group (Table; Figure 1b). Nevertheless, the mean period of survival after reaching this high blood pressure level was 130 ± 42 days as compared with 4 ± 2 days in control animals (P < 0.05), indicating that hypertension in itself was not acutely harmful under conditions of ETA-receptor blockade. In the A70early group, SBP had already become significantly lower than control animals at day 14 and reached a lower maximal level (Table; P < 0.05 versus control and A35early groups). The mean period of survival after reaching this blood pressure level was 72 ± 14 days, again significantly increased compared with the control group (P < 0.05). From day 70 until day 90, SBP was significantly different from the A35early group (Figure 1b).

Proteinuria increased in the control group, from 11 ± 5 mg/d at day 0 to nearly 400 mg/d (Table). As was the case for hypertension, the development of proteinuria was dose-dependently delayed by A127722 treatment (Figure 1c). In the A35early group, proteinuria became significantly lower than the control group at day 28 (Figure 1c) but also reached a maximal level of approximately 400 mg/d shortly before
death (Table). In the A70LATE group, proteinuria became significantly lower than in the control group at day 28; despite a small transient increase (64 ± 11; P < 0.05 versus control and A35 early groups; Table), the terminal level was as low as baseline (Table; P < 0.05 versus control and A35 early groups). At day 84 proteinuria was significantly lower than in the A35 early group (Figure 2c).

Histology
With the T2W-MRI modality used for brain scanning, it is known that hemorrhagic patches are hypointense due to the T2-shortening effect of iron. The hypointense pixels on the MR images (Figure 2c) corresponded to cerebral hemorrhages on the HE- and Fe-stained cerebral histological sections (Figure 2f). To examine whether the hemorrhages were a result of a general toxic effect or a local effect in the brain, we also examined lungs, kidney, and liver for the presence of hemorrhage. However, no such hemorrhage was found.

Typical examples of the various degrees of glomerular damage are shown in Figure 3. Widespread glomerular injury was observed in the control animals. Glomerular damage was significantly reduced in the A70 early group (Table).

Late-Onset Treatment
Edema developed at a mean of 43 days after the initiation of salt loading. The percentage of hyperintense pixels at this time point was 11.67 ± 2.44%. Subsequent initiation of treatment did not prolong survival (Table). In both treated groups the terminal level of hyperintense pixels was significantly reduced as compared with control animals (Table). However, as a group this level was significantly increased (A35 late + A70 late = 10.92 ± 1.35%) in comparison to the early treated animals (P < 0.05; A35 early + A70 early = 6.57 ± 0.68%). This difference, in comparison to early treatment, was partly due to larger ventricles (Figure 2d), because the edema had practically disappeared in 4 of the 8 rats. SBP, proteinuria, and glomerular index were not different after the initiation of either low or high dose treatment (Table).

Discussion
In the present study we established that ET-1 is important in the development of hypertension and in target-organ damage in salt-loaded SHRSP, a model of malignant hypertension. However, ETα-receptor blockade, in contrast to ACE inhibition, is not effective once organ damage has been established. The implication of this finding is that ET plays a role in the genesis of hypertension and proteinuria but not in the maintenance of established target-organ damage.

Early Therapy
ETA receptor blockade completely prevented the development of cerebral edema in this model, similarly to results found with a calcium channel blocker.20 Both maneuvers decrease blood pressure, which may well contribute to this protection. However, nonhemodynamic effects of ETα-receptor blockade may also be involved, because in marked contrast to the dose-dependent amelioration of the hypertension, the development of cerebral edema was prevented at both the low and high doses. Furthermore, cerebral edema remained absent in the low-dose group for many months despite blood pressures that were no different from those observed terminally in control animals. Indeed, we and others have shown that a decrease in blood pressure is not necessary to prevent the development of cerebral edema in the SHRSP. ACE inhibition15,21 and dietary potassium administration,22 with or only a small reduction in blood pressure, substantially prolonged survival in salt-loaded SHRSP. In contrast, a thromboxane A2 synthase inhibitor,23 hydralazine, and diuretics,24 which all reduced blood pressure, did not prevent cerebral edema or significantly prolong survival.

Because ET-1 mediates some of the renal hemodynamic25 and mitogenic26 effects of angiotensin II, and because angiotensin II increases ET-1 levels in rat kidney via an ETα-receptor–coupled mechanism,27 it was also interesting to explore whether ETα-receptor antagonism is a useful protective strategy for the kidney in this model. When ETα-receptor antagonism was started before the occurrence of renal lesions, the increases in blood pressure and proteinuria characteristic of the model were, depending on the dose, partially or totally prevented, suggesting involvement of ET. The magnitude of the effect of the ETα-receptor blocker in preventing the development of hypertension and proteinuria was in agreement with studies in salt-loaded SHRSP, in which peptide antagonists of the ETα receptor were administered for approximately 6 weeks12–14 and with studies in non–salt-loaded

### Table: Survival of SHRSP After Start of Salt Loading and the Maximal and Terminal Values of SBP and Proteinuria (UpV) in Control Animals and during Low- and High-dose ETα-receptor Blockade

<table>
<thead>
<tr>
<th>Group</th>
<th>Rats, n</th>
<th>Median Survival, d (range)</th>
<th>Cerebral Hyperintensity (Terminal), % pixels</th>
<th>SBP, mm Hg</th>
<th>UpV, mg/d</th>
<th>Glomerular Damage Index (Terminal), Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>54 (32–80)</td>
<td>19.0 ± 2.9</td>
<td>270 ± 12</td>
<td>289 ± 7</td>
<td>317 ± 67</td>
</tr>
<tr>
<td>A35 early</td>
<td>7</td>
<td>233 (92–407)*</td>
<td>5.8 ± 1.0*</td>
<td>214 ± 19*</td>
<td>267 ± 2</td>
<td>372 ± 43</td>
</tr>
<tr>
<td>A70 early</td>
<td>7</td>
<td>124 (97–169)*</td>
<td>7.4 ± 0.9*</td>
<td>178 ± 15*</td>
<td>239 ± 11*†</td>
<td>12 ± 4*†</td>
</tr>
<tr>
<td>A35 late</td>
<td>4</td>
<td>66 (54–74)</td>
<td>10.6 ± 2.3*</td>
<td>272 ± 9</td>
<td>279 ± 6</td>
<td>436 ± 114</td>
</tr>
<tr>
<td>A70 late</td>
<td>4</td>
<td>54 (51–55)</td>
<td>11.2 ± 1.7*</td>
<td>286 ± 6</td>
<td>285 ± 7</td>
<td>198 ± 13</td>
</tr>
</tbody>
</table>

*P < 0.05 vs control; †P < 0.05 vs 35 mg · kg⁻¹ · d⁻¹.

Treatment was initiated together with the start of salt loading, A35 early and A70 early, and after the first detection of cerebral edema, A35 late and A70 late. Values are mean ± SEM, except as noted.
Figure 2. The effect of initiation of ET_A receptor blockade at the start of salt loading (columns b and c) and after the development of cerebral edema (column d) as illustrated by successive T2-weighted MR images (pixel resolution, 0.31×0.31 mm²; slice thickness, 1 mm) positioned to the stereotaxic reference point bregma and corresponding histological sections. In all columns, day 0 is defined as the start of salt loading. Column a, Control group (bregma 2.20). At day 46 this rat developed a hyperintense spot, ie, vasogenic cerebral edema, in the right frontal cortex from and it spread to the adjacent tissue. Finally, at day 72 a hypointense spot, ie, hemorrhage, appeared in the originally affected area. Column b, A35 early (bregma 2.20). No cerebral edema was detected in these rats during the whole experiment. Note the enlarged ventricles. Column c, A70 early (bregma 2.30). As in A35 early group, no cerebral edema appeared during the experiment. At day 134, 4 days before natural death occurred, this rat developed hemorrhages in the left and right caudate putamen, which subsequently spread in time (day 137). Note the enlarged lateral ventricles. Column d, A70 late (bregma 2.30). After late-onset treatment, edema practically disappeared in 4 of the 8 rats. The rat in this example developed cerebral edema at day +46. Cerebral edema decreased, but the lateral ventricle size increased. e, Histological section of a hyperintense area in the (right-side) white matter of a control rat showing multiple extracellular vacuoles pointing to the presence of edema. f, Histological section of a hypointense area in the left caudate putamen of the A70 early rat showing multiple hemorrhages. HE; magnification, ×500.
SHRSP, in which vascular hypertensive damage was ameliorated.\textsuperscript{28,29} Because voltage-operated calcium channels probably have an important role in the signal transduction after ETA-receptor activation,\textsuperscript{30} it is not surprising that calcium channel blockers had similar preventive effects on hypertension and renal damage in this model.\textsuperscript{20} The dependency of proteinuria on blood pressure under conditions of ETA-receptor blockade was apparent, because in the low-dose group proteinuria became high after approximately 3 months, parallel to blood pressure. In contrast, during ACE inhibition in salt-loaded SHRSP the antiproteinuric effect is not accompanied by a change in blood pressure.\textsuperscript{15,21,31} Apparently, the proteinuric effect of ET-1 is largely mediated via an increase in blood pressure, whereas angiotensin II exerts its renal pathogenic effect in this model primarily via local effects. Furthermore, the absence of an antihypertensive effect during ACE inhibition may indicate that in conscious SHRSP in the salt-loaded condition the hemodynamic actions of ET-1 and angiotensin II are independent.

Although hypertension and cerebral injury are the most important factors contributing to mortality in control SHRSP, it is most likely that renal damage was the main cause of death in the low-dose (35 mg · kg\textsuperscript{-1} · d\textsuperscript{-1}) early-onset group, because cerebral edema did not occur and blood pressure was constantly high, whereas maximum proteinuria was reached just before natural death occurred. In the high-dose (70 mg · kg\textsuperscript{-1} · d\textsuperscript{-1}) early-onset group, the terminal values of hypertension, proteinuria, and glomerular sclerosis were the lowest of all treated groups, and cerebral edema was absent. However, these rats died prematurely from cerebral hemorrhage, mainly in the caudate putamen. We have no explanation for the observed hemorrhage. It could be the result of a

**Figure 3.** Histological sections of glomeruli with different degrees of sclerosis. a, Normal glomerulus (score of 0). b, Segmental mesangial sclerosis with adhesion (relatively extensive changes, upper limit of score 1). c, Global glomerular sclerosis with total obsolescence of capillaries (score of 2). d, Malignant hypertensive lesion with fibrinoid change of the entire glomerular tuft (score of 2). HE; magnification, ×500.
direct toxic effect of a high concentration of A127722. This seems unlikely because other organs lacked spontaneous hemorrhages, but a specific cerebrotoxic effect cannot be excluded. Alternatively, displacement of ET-1 from ETA receptors and subsequent nitric oxide generation could be involved.\textsuperscript{32} Nitric oxide may lead to decreased platelet aggregation\textsuperscript{33} and thus increase the risk of hemorrhagic stroke.\textsuperscript{34} Indeed, intracarotid administration of a high dose of ET-1 leads to a decrease in platelet aggregation.\textsuperscript{35} However, the low affinity of A127722 for the ETB receptor has specifically been shown in membranes prepared from the cerebellum.\textsuperscript{16} Thus, the relevance of these observations in rats to the therapeutic use of ET\textsubscript{A}-receptor blockade in hypertension is uncertain. Higher doses of A127722 may have deleterious effects, and possibly greater benefit can be obtained with intermediate dosages.

**Late Therapy**

In a recent study we found that in salt-loaded SHRSP ACE inhibition had practically no effect on blood pressure but caused complete regression of established cerebral edema and urine protein excretion and markedly prolonged survival.\textsuperscript{15} However, in the present study we observed that once cerebral edema was present, ET\textsubscript{A}-receptor blockade did not prolong survival or reduce blood pressure or proteinuria. At this late stage, neither ACE inhibition nor ET\textsubscript{A}-receptor blockade exerts an antihypertensive effect, indicating that when renal damage and salt loading are concomitant, bypassing of both systems is necessary to maintain sodium balance. The effects on cerebral edema were inconsistent. Interestingly, a benzothiazepine calcium antagonist was able to dose-dependently reduce neurological symptoms and histological changes in brain and kidney,\textsuperscript{36} implying that agonists other than ET-1 activate these channels. It is well known that ACE inhibition has direct effects on the kidney and can reduce proteinuria without affecting blood pressure.\textsuperscript{37} This is probably due to upregulation of various components of the renin-angiotensin system in the diseased kidney. In contrast, upregulation of ETA receptors was not observed in the remnant kidney, a model of hypertensive renal injury.\textsuperscript{2} This may partly explain our observation that the ETA receptor is not crucial in the maintenance of manifest target-organ damage in SHRSP. Such damage, once established, apparently becomes independent of the ET\textsubscript{A} receptor and more dependent on the local effects of angiotensin II.

In conclusion, chronic blockade of the ETA receptor in salt-loaded SHRSP with a nonpeptide antagonist markedly increased survival, attenuated the development of hypertension, and prevented cerebral edema and renal damage. This is in contrast to the well-known protective effects of ACE inhibition in this model that occur independently of a decrease in blood pressure. Moreover, in contrast to our previous experience with ACE inhibition, when treatment was started after the development of cerebral edema no important beneficial effects were seen.

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