Renal Vasoconstriction by the Endothelial Cell-Derived Peptide Endothelin in Spontaneously Hypertensive Rats


The effects of endothelin on systemic and renal hemodynamics in anesthetized spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats were examined. Endothelin (500 ng i.v. + 1,000 ng/hr per 300-g rat) elevated mean blood pressure by 13% (p<0.02) and decreased renal blood flow by 71% and glomerular filtration rate by 66% (both p<0.01), resulting in a 430% (p<0.05) increase in renal vascular resistance (RVR) in SHR. This rise in blood pressure was associated with a significant increase in hematocrit (+8%), but a decrease in urinary sodium excretion (-51%). This dose of endothelin reduced cardiac output by 40% (p<0.001) and brought about a 96% (p<0.01) rise in systemic vascular resistance (SVR). However, the SVR increase was significantly smaller than the RVR increase. These changes in systemic and renal hemodynamics were observed in a dose-dependent manner, and the degrees of change did not differ between the two strains. Additional infusion of atrial natriuretic peptide (0.33 μg/kg/min) into SHR completely reversed the changes in blood pressure and renal hemodynamics caused by endothelin, resulting in pronounced natriuresis (+760%). The renal vascular casting study revealed that endothelin mainly constricted the arcuate and interlobular arteries, as well as afferent arterioles. These results suggest that endothelin may be involved in blood pressure and body fluid volume regulation through systemic and renal vasoconstriction. (Circulation Research 1989;65:1370-1379)

A potent vasoconstricting substance has recently been isolated from the culture medium of porcine aortic endothelial cells. This substance was found to be a 21-amino acid peptide and has been designated endothelin. Rat and human endothelin has also been sequenced by use of complementary DNAs (cDNAs) selected from a rat genomic library and a human placenta library, respectively, and has been shown to be one of the most potent in vitro vasoconstrictors known. Accordingly, this peptide may potentially be involved in some pathophysiologic states in which vascular tone is elevated.

Excessive vascular resistance has been commonly observed as a dominant hemodynamic abnormality in patients with established essential hypertension. An increase in renal vascular resistance is also consistently found in experimental and human hypertension. In this context, it is worth investigating the in vivo effects of this newly discovered peptide on systemic vascular resistance (SVR) and renal vascular resistance (RVR).

In the present study, we examined the effects of endothelin on the systemic and renal hemodynamics in spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats. We attempted to locate the sites of action in renal vessels by use of the vascular casting technique. We also compared the renal effects of endothelin with those of other vasoactive substances.

Materials and Methods

Study I: Renal Effects of Endothelin

Male SHR and WKY rats weighing about 300 g (12-13 weeks of age) were anesthetized with inactin...
STUDY I: Renal Effects of Endothelin

- PAH+ Inulin (0.6 ml/hr)
- Vehicle (0.5 ml/hr)
- EDT or NE (0.5 ml/hr)

20 min U1 20 min U2 6 min ED7 inj 20 min U3

STUDY II: Systemic Effects of Endothelin

- Vehicle (1.2 ml/hr) EDT (1.2 ml/hr)

STUDY III: Sites of Action of Endothelin

- Vehicle (1.2 ml/hr)
- ANP (0.5 ml/hr)

FIGURE 1. Experimental protocol showing time schedule and infusion volume. PAH, p-aminohippuric acid; EDT, endothelin; NE, norepinephrine; U, urine collection; inj, bolus intravenous injection; ANP, atrial natriuretic peptide; CO, cardiac output measurement; ligation, aortic ligation.

(100 mg/kg i.p.) and cannulated through the trachea, right carotid artery, jugular vein, and bladder. Experimental protocol is shown in Figure 1. Two silicone cannulas were inserted into the jugular vein. A bolus injection of lactated Ringer's solution containing 10 μCi each of 14C-methoxy-inulin and 3H-p-aminohippuric acid (PAH) was followed by continuous infusion of both agents through one of the two jugular vein cannulas at a rate of 10 μCi/hr (0.6 ml/hr). Physiological saline was infused at 0.6 ml/hr through the other jugular vein cannula. Accordingly, the total hourly fluid replacement rate was 1.2 ml/hr. After a 60-minute equilibration period, two baseline urine collections were taken 20 minutes apart. Thereafter, endothelin was administered through the saline cannula. Porcine endothelin (Peptide Institute, Osaka, Japan) was dissolved in 10 mM phosphate buffered saline (pH 7.4) with 0.01% bovine serum albumin. The injected dose of endothelin was 500, 250, 125, 62.5, or 0 (vehicle) ng, followed by continuous infusion of endothelin at a rate of 1,000, 500, 250, 125, or 0 ng/hr, respectively, to maintain blood pressure at a plateau level. Each dosage group consisted of five SHR and five WKY rats. Urine collection was resumed 5 minutes after endothelin injection and was continued for 20 minutes. At the midpoint of the urine collection, 0.5 ml blood was drawn through the arterial line for PAH, inulin, and chemical measurements; this blood was immediately replaced by the same volume of heparinized blood from other donor (WKY) rats. Mean blood pressure (MBP) and heart rate (HR) were measured with a Statham pressure transducer (Gould, Cleveland, Ohio). By use of a three-way stopcock, central venous pressure (CVP) was monitored via the jugular vein cannula for PAH and inulin infusion. Urine volume was determined by weight, sodium concentration in the plasma and urine by flame photometry, and plasma total protein concentration by the modified Lowry method. PAH and inulin concentrations in 0.1 ml plasma and 0.03 ml urine were simultaneously measured by use of a liquid scintillation counter. Effective renal blood flow (RBF) was obtained by PAH clearance and hematocrit, and glomerular filtration rate (GFR) was obtained by inulin clearance. RVR was calculated as MBP/RBF.

We also examined changes in the plasma concentration of atrial natriuretic peptide (ANP) caused by endothelin administration. In five WKY rats, MBP, CVP, and HR were monitored. Before and 10 minutes after administration of 250 ng endothelin, 1 ml arterial blood was collected and replaced by the same volume of blood from donor rats. The plasma concentration of immunoreactive ANP was determined by the method previously reported.11 For study of the interaction between endothelin and ANP, α-rat ANP (Protein Research Foundation, Osaka, Japan) was administered to endothelin-infused rats, and blood pressure and renal function were determined as shown in Figure 1. In five SHR and five WKY rats that received 500 ng endothelin, α-rat ANP was infused into the jugular vein cannula at 0.33 ng/kg/min 20 minutes after endothelin administration. Urine was collected from 0-5 and 5-10 minutes after ANP infusion. The effects of norepinephrine infusion (200 ng/kg/min) on renal circulation were also compared in five SHR and five WKY rats under conditions similar to those for the endothelin studies.

Study II: Cardiovascular Effects of Endothelin

The effects of endothelin on systemic hemodynamics in another group of SHR and WKY rats (n=5 for each tested dosage) under the same conditions as in study I were examined. Vehicle or endothelin (125 or 500 ng) was injected as a bolus, and then endothelin was continuously infused at a rate of 0, 250, or 1,000 ng/hr, respectively, through one of the two jugular vein cannulas. Before and 10 minutes after endothelin administration, blood pressure, HR, CVP, and cardiac output (CO) were determined (Figure 1). The CO was measured by a dye-dilution method by use of a microcuvette, as...
The vessels observed were selected according to microscopy (model S-650, Hitachi, Ibaraki, Japan). The glomerular tuft were photographed by scanning electron microscopy (model SMZ-2T, Nikon, Tokyo, Japan). The renal arcuate and interlobular arterioles were then observed stereomicroscopically (model S-650, Hitachi, Ibaraki, Japan). The vessels observed were selected according to two criteria: 1) Both intact afferent and efferent arterioles were attached to the superficial glomeruli, and 2) each arteriole could be easily identified. The identification of each arteriole was based on the finding that the afferent arteriole branched from the interlobular artery, whereas the efferent arterioles branched to the peritubular capillary network. The diameters of the arterioles at three points at equal intervals within 50 μm from each vascular pole of the glomerulus were measured on photographs and then averaged. The effects on the diameters of vehicle, endothelin (500 ng), or α-rat ANP (0.33 μg/kg/min) concomitant with endothelin infusion were compared. The microscopist was unaware of the regimen. A total of 25 arterioles was observed in each group (i.e., five glomeruli from each rat, five rats [kidneys] from each group).

Statistics

The effects of the agents administered were assessed by the paired t test. The comparison of means between two groups was made by non-paired t test. Differences in means among three groups were analyzed by the modified t test on the basis of analysis of variance (ANOVA) and are expressed as mean±SEM. The statistical significance level was set at p<0.05.

Results

Study I: Renal Effects of Endothelin

Blood pressure in SHR transiently fell immediately after endothelin treatment and then gradually increased. Blood pressure reached a peak within 5 minutes after the injection, and the plateau values were maintained for at least 30 minutes with this procedure. The increases in MBP were dose-dependent, and 500 ng endothelin elevated MBP by 13%, as shown in Figure 2. This rise in MBP was associated with marked reductions in RBF of 71% and in GFR of 66% (Figure 2). Basal values of MBP, GFR, and RBF are presented in Table 1. Figure 3 and Table 2 demonstrate urinary sodium excretion, CVP, hematocrit, and plasma concentrations of total protein and sodium before and after endothelin administration. The highest dosage of endothelin tested substantially reduced urinary sodium excretion, whereas it decreased CVP and increased hematocrit and total protein concentration. On the other hand, the plasma concentration of sodium did not change. Figure 4 shows the degrees of changes in RVR by endothelin in SHR and WKY rats. These changes were also dose-dependent within dosages tested, although the values were comparable between the two strains.

Norepinephrine infusion into SHR at 200 ng/kg/min (1.1 nmol/kg/min) elevated MBP by 15%. RBF and GFR were significantly decreased by 41% (p<0.01) and 14% (p<0.01), respectively, during norepinephrine infusion, resulting in an increase in RVR of 96% (p<0.02). Similar changes in these
was significantly greater than that caused by norepinephrine (Figure 4).

Endothelin (250 ng) increased the plasma concentration of ANP from 76 ± 6 to 87 ± 7 pg/ml (p < 0.02). This elevation was accompanied by significant increases in MBP (+7.2%, p < 0.02) and hematocrit (+5.3%, p < 0.01) but decreases in heart rate (−3.6%, p < 0.05) and CVP (−1.0 mm Hg, p < 0.05). Figure 5 shows the effects of ANP on endothelin-induced changes in renal function of SHR. Additional infusion of α-antagonist ANP to endothelin significantly increased RBF, GFR, and urinary sodium excretion, which had all been decreased by endothelin, and decreased MBP and RVR (~55%, p < 0.01). Similar effects of ANP on endothelin-induced renal vasoconstriction were observed in WKY rats (data not shown).

**Study II: Cardiovascular Effects of Endothelin**

Figure 6 shows the effects of endothelin on systemic hemodynamics. In study II, MBP was again increased to similar degrees in SHR and WKY rats during endothelin infusion. CO in SHR was reduced by about 40% after 500 ng endothelin, resulting in a substantial increase in SVR (Figure 4). HR was slightly decreased by 5%. Thus, stroke volume was also reduced by about 40% (p < 0.001). These changes in systemic hemodynamics were also observed in a dose-dependent fashion. However, when the increases in SVR and RVR (study I) due to the highest dosage of endothelin were compared, the change was significantly smaller in SVR than in RVR (Figure 4). These differences in vascular response were observed in both SHR and WKY rats. Although basal blood pressure and SVR were greater in SHR than in WKY rats (Table 3), the

### TABLE 1. Basal Values of Renal Hemodynamics Before Endothelin Infusion in SHR and WKY

<table>
<thead>
<tr>
<th></th>
<th>Endothelin (ng/300-g rat)</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>171±8⁺</td>
</tr>
<tr>
<td>WKY</td>
<td>127±5</td>
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<tr>
<td>GFR (ml/min/100 g)</td>
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<tr>
<td>SHR</td>
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</tr>
<tr>
<td>WKY</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td>RBF (ml/min/100 g)</td>
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</tr>
<tr>
<td>SHR</td>
<td>4.0±0.4</td>
</tr>
<tr>
<td>WKY</td>
<td>3.8±0.5</td>
</tr>
<tr>
<td>RVR (mm Hg · min · 100 g/ml)</td>
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<tr>
<td>SHR</td>
<td>45±3‡</td>
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<tr>
<td>WKY</td>
<td>34±3</td>
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</tbody>
</table>

Values are expressed as mean ± SEM; n = 5 for each group. SHR, spontaneously hypertensive rats; WKY, Wistar-Kyoto rats; MBP, mean blood pressure; GFR, glomerular filtration rate; RBF, renal blood flow; RVR, renal vascular resistance.

⁺p < 0.01 vs. WKY.
⁻p < 0.001 vs. WKY.
¨p < 0.05 vs. WKY.
¶p < 0.02 vs. WKY.
degrees of endothelin-induced changes in CO and SVR did not differ between the two strains.

Study III: Site of Action of Endothelin

Figures 7 and 8 demonstrate the results of the renal casting study during vehicle or endothelin infusion. Endothelin caused segmental constriction in the arcurate and interlobular arteries (Figure 7). Figure 8 shows the afferent arterioles and glomerulus during vehicle or endothelin infusion. The afferent arteriole was more constricted during endothelin infusion than during vehicle infusion. The diameters of the afferent and efferent arterioles and their ratios are summarized in Figure 9. The diameter of the afferent arterioles was significantly smaller in the endothelin group than in the control group. However, this decreased diameter returned to the control level with the addition of α-rat ANP to endothelin. On the other hand, the efferent diameter was not influenced by endothelin. The ratio of the afferent/efferent arteriole tended to be decreased by endothelin and restored by ANP; however, these changes in the ratio were not statistically significant.

Discussion

In the present study, endothelin was found to dose-dependently increase MBP. This pressor effect was associated with decreases in RBF, GFR, and urinary sodium excretion, suggesting that this peptide causes vigorous renal vasoconstriction. These findings are consistent with recent reports. Wright and Fozard15 demonstrated that a bolus injection of endothelin caused a sustained decrease in RBF in ganglion-blocked SHR. Firth et al16 also reported pronounced renal vasoconstriction and GFR reduc-

TABLE 2. Effects of Endothelin on Major Volume Factors Before and During Endothelin Administration in SHR and WKY

<table>
<thead>
<tr>
<th>Endothelin (ng/300-g rat)</th>
<th>0</th>
<th>62.5</th>
<th>125</th>
<th>250</th>
<th>0</th>
<th>62.5</th>
<th>125</th>
<th>250</th>
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<tbody>
<tr>
<td>UNaV (nEq/min/100 g)</td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>96±15</td>
<td>72±6</td>
<td>56±13</td>
<td>106±33</td>
<td>62±25</td>
<td>70±5</td>
<td>73±17</td>
<td>101±17</td>
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<tr>
<td>Endothelin</td>
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<td>72±19</td>
<td>98±42</td>
<td>65±9*</td>
<td>60±16</td>
<td>119±32</td>
<td>72±13</td>
<td>89±16*</td>
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<tr>
<td>CVP (mm Hg)</td>
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<tr>
<td>Baseline</td>
<td>0.2±0.9</td>
<td>0.9±0.6</td>
<td>0.5±0.8</td>
<td>0.7±0.7</td>
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<td>1.0±0.6</td>
<td>0.4±1.3</td>
<td>0.5±0.3</td>
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<td>Endothelin</td>
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<td>0.8±0.6</td>
<td>0.3±1.7</td>
<td>0.1±0.6*</td>
<td>0.3±2.3</td>
<td>0.5±0.5</td>
<td>0.2±1.2</td>
<td>0.2±0.2*</td>
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<tr>
<td>Hct (%)</td>
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<tr>
<td>Baseline</td>
<td>49±1</td>
<td>54±2</td>
<td>50±1</td>
<td>52±1</td>
<td>50±1</td>
<td>49±2</td>
<td>48±1</td>
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<tr>
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<td>49±2</td>
<td>56±2</td>
<td>52±1</td>
<td>56±3*</td>
<td>49±1</td>
<td>50±2</td>
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<td>TP (g/dl)</td>
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<tr>
<td>Baseline</td>
<td>5.7±0.5</td>
<td>6.2±0.6</td>
<td>6.3±0.4</td>
<td>6.2±0.3</td>
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<td>6.5±0.8</td>
<td>6.6±0.4</td>
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<tr>
<td>Endothelin</td>
<td>5.7±0.4</td>
<td>6.2±0.6</td>
<td>6.4±0.3</td>
<td>7.0±0.6*</td>
<td>5.8±0.3</td>
<td>6.5±0.8</td>
<td>6.8±0.4</td>
<td>7.3±0.2*</td>
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<tr>
<td>Plasma sodium concentration (mEq/l)</td>
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<tr>
<td>Baseline</td>
<td>132±4</td>
<td>132±6</td>
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<tr>
<td>Endothelin</td>
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<td>132±7</td>
<td>133±2</td>
<td>138±4</td>
<td>137±3</td>
<td>138±7</td>
<td>130±4</td>
<td>139±4</td>
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</table>

Values are expressed as mean±SEM. SHR, spontaneously hypertensive rats; WKY, Wistar-Kyoto rats; UNaV, urinary sodium excretion; CVP, central venous pressure; Hct, hematocrit; TP, plasma concentration of total protein.

*p<0.05 vs. baseline.
tion in the isolated rat kidney during perfusion with an endothelin solution. To confirm these findings, we examined the intrarenal sites of action of endothelin by means of a renal vascular casting technique. The measurement of vessel diameters by use of renal casts has been applied to the evaluation of vascular tone in rat afferent arterioles. It has been reported that such a perfusion-fixation technique enables reproducible measurements and that a smaller afferent diameter is noted in SHR and in normotensive rats receiving norepinephrine or angiotensin II. In addition to the afferent arterioles, we extended the observation to the renal arcuate and interlobular arteries and efferent arterioles. We found that endothelin greatly constricted the arcuate and interlobular arteries and afferent arterioles, whereas the effect on the efferent vessels was not obvious.

In our preparation, it seems likely that the sympathetic nervous system and renin-angiotensin system in the rats of the present study were activated at least by the anesthesia. Accordingly, if the efferent vasoconstriction caused by both norepinephrine and angiotensin II occurs before endothelin administration, the response of the efferent arterioles to the peptide may be attenuated. However, in the present study, endothelin (500 ng) caused parallel decreases in GFR (−66%) with RBF (−71%), whereas norepinephrine (200 ng/kg/min) caused a relatively small decrease in GFR (−14%) compared with that in RBF (−41%), suggesting that norepi-
nephrine brought about relative conservation of the GFR by constricting the efferent arterioles. This finding indicates that the efferent arterioles observed in the present study are still responsive to vasoconstricting substances, even if attenuated.

Such heterogeneity of the renal vascular effects has been shown in many renal vasoactive substances, such as angiotensin II and dopamine. Vasoconstriction due to angiotensin II is observed in the efferent arterioles but not in the afferent arterioles, although conflicting results have been reported. Dopamine also preferentially dilates preglomerular vessels.

The mechanisms whereby the vasoconstricting effects of endothelin are predominant in renal (particularly preglomerular) vasculature are not clear. However, it is known that renal vascular resistance is highly dependent on the extracellular Ca\(^{2+}\) concentration. It has been shown that various kinds of Ca\(^{2+}\) antagonists such as verapamil, diltiazem, and dihydropyridine compounds preferentially dilate renal preglomerular vessels. Loutzenhiser et al demonstrated that nisoldipine, a dihydropyridine compound, brought about the recov-

![Figure 7](http://circres.ahajournals.org/)

**Figure 7.** Renal vascular casting of arcuate and interlobular arteries during vehicle (C, upper panel) and endothelin infusion (E, lower panel). Arrows indicate segmental constriction in arcuate (middle) and interlobular arteries (lower). Infusion dose of endothelin was 500 ng bolus+1,000 ng/hr infusion per 300-g rat.
ery of a norepinephrine-induced GFR reduction by preferential dilatation of the preglomerular vessels. This compound was less effective in the postglomerular vasoconstriction brought about by norepinephrine. Furthermore, Fleming et al. have shown that nitrendipine, another dihydropyridine compound, predominantly dilates the arcuate and interlobular arteries and afferent arterioles near the interlobular artery, whereas acetylcholine dilates both preglomerular and postglomerular vessels in the hydronephrotic kidney. This suggests that the tone of preglomerular vessels is more dependent on the entry of extracellular Ca\(^{2+}\) than is the tone of efferent arterioles. The intracellular mechanisms of endothelin-induced vasoconstriction have not yet been fully elucidated. However, the removal of

\[
\begin{array}{|c|c|c|}
\hline
\text{Afferent (μm)} & \text{Efferent (μm)} & \text{A/E} \\
\hline
0 & 10 & 1.4 \\
5 & 15 & 1.2 \\
10 & 20 & 1.0 \\
\hline
\end{array}
\]

\(c:\) Control, \(e:\) Endothelin

\[
\begin{array}{|c|c|c|}
\hline
\text{C} & \text{E} & \text{E+ANP} \\
\hline
0 & 10 & 1.4 \\
5 & 15 & 1.2 \\
10 & 20 & 1.0 \\
\hline
\end{array}
\]

\[
\begin{array}{|c|c|c|}
\hline
\text{C} & \text{E} & \text{E+ANP} \\
\hline
0 & 10 & 1.4 \\
5 & 15 & 1.2 \\
10 & 20 & 1.0 \\
\hline
\end{array}
\]

\text{FIGURE 8. Renal vascular casting of afferent (aa) and efferent arterioles (ea) and glomerulus during vehicle (C, upper panel) and endothelin infusion (E, lower panel). Infusion dose of endothelin was 500 ng bolus+1,000 ng/hr infusion per 300-g rat.}

\text{FIGURE 9. Diameters of afferent and efferent arterioles and ratio of afferent to efferent diameter during infusion of vehicle (C), endothelin (E, 500 ng bolus+1,000 ng/hr infusion per 300-g rat), and endothelin with atrial natriuretic peptide (E+ANP, 0.33 μg/kg/min).}
was supported by the increased afferent diameter in the casting study. It is known that ANP inhibits the vasodilative effects of ANP and concurrently constricts the afferent arterioles and concurrently constricts renal vasoconstrictor and antinatriuretic effects of ANP. ANP also inhibits intracellular Ca\(^{2+}\) release by norepinephrine. Such mechanisms may underlie the renal antagonistic action of ANP against endothelin.

In the present study, endothelin elevated the plasma concentration of ANP without increasing the CVP or HR. It has been reported that either an increase in HR or CVP or a decrease in hematocrit due to plasma volume expansion stimulates the secretion of ANP. From our results, it seems unlikely that endothelin raises the plasma concentration of ANP by increasing atrial stretch. An increase in intracellular calcium concentration of the atrial tissue is considered to be another potent stimulatory factor for ANP release. Taking into consideration the fact that endothelin functions as a calcium agonist, this peptide may augment ANP release from the atria directly through an intracellular mechanism. This is compatible with the recent report that endothelin increased the secretion of ANP from rat cultured atrial cells.

Vascular responses to endothelin were not different between SHR and WKY rats. Since many factors such as vascular hypertrophy, the intrinsic activity of endothelin, and consequent changes in the endothelin receptors, as well as hypertensive endothelial damage, may influence vascular reactivity to this peptide, the exact role of endothelin in the hypertensive state of SHR cannot be concluded from this study. However, increased renal vascular resistance in essential hypertensive patients and SHR is believed to be attributable to the increase in preglomerular resistance. In this context, the action of this peptide may be one of the mechanisms involved in the augmented preglomerular vascular tone observed in hypertension. Further studies are needed to explore the involvement of endothelin in the development of hypertension.

Although it has not been determined whether or not endothelin is a circulating hormone, the potent vascular effects of endothelin observed in the present study are most likely pharmacological in nature. However, if endothelin is sufficiently locally active, this peptide may contribute to blood pressure and volume regulation through systemic and renal vasoconstriction, as well as via the resultant antinatriuresis and transvascular fluid leakage. Vascular endothelial cells are believed to control vascular smooth muscle tone mainly through dilative mechanisms. This study suggests that endothelial vasoconstrictor mechanisms should also be taken into consideration in the understanding of blood pressure and body fluid volume homeostasis.

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