Characteristics of Pressor Response to Endothelin in Spontaneously Hypertensive and Wistar-Kyoto Rats

Takashi Miyauchi, Tomohisa Ishikawa, Yoko Tomobe, Masashi Yanagisawa, Sadao Kimura, Yasuro Sugishita, Iwao Ito, Katsutoshi Goto, and Tomoh Masaki

Endothelin, an endothelium-derived vasoconstrictor peptide, and angiotensin II were intravenously injected into the femoral vein of normotensive Wistar-Kyoto (WKY) rats that had been anesthetized with urethane. Blood pressure and heart rate were recorded from a cannula inserted into the carotid artery. All experiments were carried out after treatment with adrenergic and cholinergic antagonists. Endothelin showed a potent, dose-dependent pressor action. The dose-response relations for the increase in blood pressure of rats receiving endothelin were comparable with those of rats receiving angiotensin II. However, endothelin showed far more long-lasting effects. Endothelin-induced responses consisted of three phases: a rapid and transient depressor phase and then two phases of pressor (transient and long-lasting) response. Nicardipine (0.1 mg/kg), a dihydropyridine Ca²⁺ channel blocker, markedly attenuated the slow phase of the pressor response but only slightly attenuated the rapid one. The pressor action of endothelin was not inhibited by continuous infusions of saralasin, which almost abolished the angiotensin II–induced pressor response. Endothelin-induced pressor response was also not attenuated by indomethacin, a prostaglandin synthesis inhibitor. These data provide evidence that endothelin produces a unique, potent, and long-lasting pressor response, which appears to be in part related to the activation of Ca²⁺ channels. In 12-week-old spontaneously hypertensive rats (SHR), the maximal pressor response to endothelin was slightly but significantly greater than that in age-matched WKY rats, but the dose dependency of the response was approximately consistent with that in WKY rats. In contrast to the in vivo data, the vasocontractile effect of endothelin on the isolated mesenteric artery was more sensitive in 12-week-old SHR than in WKY rats, despite no differences between SHR and WKY rats at 6 weeks of age. The implication of this inconsistency is discussed. (Hypertension 1989; 14:427–434)
constrictions. We have succeeded in purification of this peptide from the culture media of porcine aortic endothelial cells and named it endothelin (ET). ET is a 21-amino acid peptide with two sets of an intrachain disulfide bond and exhibits a potent, long-lasting vasoconstrictor action on various vascular strips in vitro.\textsuperscript{14,15} Northern blot analysis with a complementary DNA (cDNA) insert of preproendothelin has demonstrated that a preproendothelin messenger RNA (mRNA) is expressed not only in the cultured endothelial cells but also in intact porcine aortic intima.\textsuperscript{14} An increase in peripheral vascular resistance can result in systemic hypertension. Since ET is a potent vasoconstrictor substance that is produced in the vascular endothelial cells, it could be supposed that ET can contribute to the abnormality of systemic blood pressure. Therefore, one of the aims of the present study was to investigate the mode of action of ET on the systemic blood pressure. The second aim was to study the significance of ET in hypertension by using the spontaneously hypertensive rat (SHR), a model of essential hypertension.

Materials and Methods

The experiments were performed with 6- and 12-week-old male Wistar-Kyoto (WKY) rats and SHR obtained from Charles River Japan Inc. (Kanagawa, Japan). Systolic blood pressure was measured with a tail-cuff sphygmomanometer (Riken Kaihatsu PS-100, Kanagawa, Japan). The following experiments were performed using a synthetic endothelin-1, which was formerly called porcine/human endothelin.\textsuperscript{16}

In Vivo Experiments

Each rat was anesthetized with urethane (1.5 g/kg i.p.), and the left carotid artery and the right femoral vein were catheterized with polyethylene tubing filled with a 0.9% saline containing heparin (10 units/ml). Arterial blood pressure and heart rate were measured from the cannula in the carotid artery with a pressure transducer (model SCK-590, Gould, Cleveland, Ohio) connected to a polygraph system (amplifier, AP-601G, Nihon Kohden; Tokyo, Japan; tachometer, AT-601G, Nihon Kohden; thermal-pen recorder, WT-687G, Nihon Kohden). All experiments were carried out after pretreatment with atropine (0.25 mg/kg i.v.), propranolol (1 mg/kg i.v.), and bunazosin (1 mg/kg i.v.). A half dose of each blocker was supplemented as necessary during the experiment (usually every 3 hours) to maintain the blocking effects. Under these conditions, both the pressor response to norepinephrine (10 nmol/kg i.v.) and the bradycardiac response to acetylcholine (10 nmol/kg i.v.) were largely suppressed. The intravenous injection of drugs was administered through the cannula in the femoral vein.

For inhibition of the action of angiotensin II (Ang II), a saline solution of saralasin ([Sar\textsuperscript{1}, Ala\textsuperscript{8}]Ang II) was continuously infused via a cannula in the left femoral vein at a rate of 5 \( \mu \)g/kg/min according to the method of Pals et al.\textsuperscript{17} To investigate the contribution of the prostaglandin (PG) syntheses, indomethacin (5 mg/kg i.v.), a cyclooxygenase inhibitor, was pretreated 30 minutes before the experiment. This dose of indomethacin abolished the depressor effect of intravenously injected arachidonic acid (3 mg/kg). This is consistent with other reports.\textsuperscript{18,19}

In Vitro Experiments

Each rat was anesthetized with sodium pentobarbital (50 mg/kg i.p.), and the superior mesenteric arteries, approximately 300 \( \mu \)m in external diameter, were dissected in a Krebs-Ringer solution of the following (mM) composition: NaCl 113, KCl 4.8, CaCl\textsubscript{2} 2.2, KH\textsubscript{2}PO\textsubscript{4} 1.2, MgSO\textsubscript{4} 1.2, NaHCO\textsubscript{3} 25, and glucose 5.5. Ring segments of 4 mm width were mounted with a stainless steel rod and a short piece of tungsten in organ baths containing the Krebs-Ringer solution (20 ml) maintained at 37\textdegree C and aerated with a mixture of 95% \textsubscript{O}2-5% \textsubscript{CO}2. The endothelium was left intact, which was verified by the endothelium-dependent vasodilator response to acetylcholine (10\textsuperscript{-8} M). The organ baths were siliconized before the experiments. The isometric contraction was measured with a transducer (TB-612T, Nihon Kohden) connected to the polygraph system. The resting tension applied was 1 g. All preparations were allowed to equilibrate for at least 1.5 hours. Before experiments, the responses to 50 mM K\textsuperscript{+} were investigated repeatedly until a steady response was obtained.

Drugs and Statistics

Drugs used were endothelin-1 and saralasin (Peptide Inst., Osaka, Japan); Ang II (Nakarai, Kyoto, Japan); bovine serum albumin (fraction V), indomethacin, and nicardipine (Sigma Chemical Co., St. Louis, Missouri); bunazosin (Eisai, Tokyo, Japan); atropine sulfate (Tanabe, Osaka, Japan); propranolol (Sumitomo, Osaka, Japan); and urethane (Tokyo Kasei, Tokyo, Japan). ET was dissolved in a phosphate-buffered saline (pH 7.4) containing 0.05% bovine serum albumin. Appropriate vehicle controls showed no effect. Indomethacin was dissolved in dimethyl sulfoxide (Wako Pure Chemicals, Osaka, Japan) and the other drugs were generally dissolved in saline.

Values are expressed as mean\pm SEM. Statistical analyses were performed with the one-way analysis of variance (ANOVA) followed by the Bonferroni method\textsuperscript{20} or the Student’s \( t \) test for unpaired values.

Results

As illustrated in Figure 1B, intravenous injection of ET caused unique changes in blood pressure in the 12-week-old WKY rats. ET, at doses of 125 and 250 pmol/kg, evoked a biphasic response. Immediately after a bolus injection of ET, the blood pressure dropped sharply, then rose slowly above the
A dose-dependent increase in the pressor response to a bolus injection of Ang II was also observed (Figure 1A). The Ang II–induced response was monophasic and returned to the baseline within several minutes. The dose-response relation for the amplitude of ET-induced response was comparable with that of Ang II (Figure 2A). Although the maximum response to Ang II was attained at a dose of 4,000 pmol/kg, the same dose of ET caused all the rats to die. For the graphic integration, the ET-induced pressor response was dramatically greater than that of Ang II (Figure 2B).

The effect of nicardipine on the pressor response to ET is illustrated in Figure 3. Nicardipine (0.1 mg/kg) was administered intravenously about 10 minutes before the dose-response study. As is seen in Figure 3B and 3D, nicardipine markedly inhibited the slow phase of the pressor response to ET, whereas the rapid one was only slightly attenuated. However, both phases of the pressor response to ET were similarly suppressed by a higher dose of nicardipine (1 mg/kg) (Figure 3C).

Continuous infusion of saralasin almost abolished the pressor effect of Ang II. In this condition, however, the ET-induced response was scarcely affected (Figure 4A) (n=4). The pressor activity of ET was also not attenuated by the indomethacin

Figure 1. Typical tracing of effects of angiotensin II (Panel A) and endothelin (Panel B) on pulsatile arterial pressure in anesthetized rats (12-week-old Wistar-Kyoto rats). Agonists were introduced by intravenous bolus injection, noted by the dots. Pressor response to endothelin at a dose of 2,000 pmol/kg lasted approximately 3 hours. BP, blood pressure; ANG II, angiotensin II; ET, endothelin.

Figure 2. Line graphs of comparisons of pressor activity between angiotensin II (ANG II) and endothelin (ET) in anesthetized rats (12-week-old Wistar-Kyoto rats). Panel A: Dose-response relations for ET-induced rises in amplitude of mean arterial pressure (○, rapid phase; ●, slow phase) and ANG II (△). The responses to ET at doses of 125 and 250 pmol/kg were composed of only a slow response phase. ΔBP, increase in blood pressure. Panel B: Dose-response relations for increases in graphic integration (ΔAREA) of mean arterial pressure produced by ET (○) and ANG II (△). Each point represents the mean of six (ET) and five (ANG II) experiments; vertical lines represent SEM. Agonist dose is shown by a log scale.
pretreatment. On the contrary, indomethacin tended to augment the pressor response. The initial depressor response was not inhibited by the indomethacin treatment (Figure 4B). (n=4).

In the prehypertensive (6-week-old) stage, no differences were recognized in both the rapid and slow phases of the pressor responses to ET between SHR and WKY rats (Figure 5, upper panel). In SHR at 12 weeks of age, the pressor effects of ET were approximately consistent with those in age-matched WKY rats (Figure 5, lower panel). At the maximum dose (2,000 pmol/kg), however, ET induced a significantly greater rise in blood pressure in SHR than in WKY rats.

Figure 6 shows the ET dose-response characteristics of the isolated mesenteric arteries from 6- and 12-week-old SHR and WKY rats. ET-induced vasoconstriction was characterized by a slowly developing and long-lasting response, which was hard to return to the initial level even after repeated washing. The sensitivity to ET was greater in 12-week-old SHR than WKY rats, but no significant difference was detected between them at 6 weeks of age. For the maximum response to ET, there was no significant difference between SHR and WKY rats (Table 1).

Discussion

The results of the present study indicate that a single intravenous injection of ET in urethane-anesthetized rats (12-week-old Wistar-Kyoto rats) had a potent pressor effect. The pressor response was significantly inhibited by the pretreatment with nicardipine, whereas indomethacin tended to augment the pressor response. The initial depressor response was not inhibited by indomethacin treatment.

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anesthetized rats elicits a characteristic response consisting of two phases (rapid depressor and slowly developing pressor) at low doses and of three phases (rapid depressor, transient pressor, and long-lasting pressor) at high doses. This response does not seem to be caused by an autonomic reflex since adrenergic and cholinergic blockers were present. It has been reported that ET induces a potent vasoconstrictor response in a variety of blood vessels isolated from various species via direct action on vascular smooth muscles. Therefore, it can be assumed that the pressor response results from a direct vasoconstrictor action of ET. ET at a dose of 2,000 pmol/kg appears to cause severe damage to the rats because more than 3 hours was required for return of arterial pressure to the baseline level. Thus, an injection of a higher dose of ET (4,000 pmol/kg) caused all the rats tested to die, mostly because of impairment of cardiac output. Simultaneously, intravenously injected ET caused a slight increase in heart rate. This is consistent with the in vitro observation that ET exerts a positive chronotropic action on the isolated right atria of guinea pigs.

ET-induced pressor response was significantly suppressed by nicardipine, a dihydropyridine Ca²⁺ channel blocker. The slow phase, which is slowly developing and long lasting, was more sensitive to nicardipine than the rapid one, suggesting that the two phases of the pressor response were induced via independent mechanisms. It has been shown, however, that Ca²⁺ channel blockers attenuate the pressor and regional vasoconstrictor actions of Ang II and norepinephrine. A bolus injection of nicardipine 0.1 mg/kg lowered the blood pressure (Figure 3, legend) and also partly suppressed the pressor actions of Ang II and norepinephrine (data not shown). However, the result that the rapid pressor response to ET is relatively resistant to nicardipine favors the possibility that the inhibition of the slow pressor response to ET is due to a specific suppressing action of nicardipine. Furthermore, it was previously demonstrated that ET exerted a slowly developing and extremely long-lasting vasoconstrictor effect on the isolated coronary arterial strips and that this effect of ET is inhibited by a small dose of nicardipine in an almost competitive manner. Thus, it is likely that nicardipine specifically suppressed the slow and long-lasting pressor action of ET. Alternatively, the inhibitory action of Ca²⁺ channel blockers on the
TABLE 1. Contractile Characteristics of Mesenteric Arteries in Response to Endothelin

<table>
<thead>
<tr>
<th>Rats</th>
<th>ED50(M) (CI)</th>
<th>Max (g)</th>
<th>K' Max (g)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-week-old</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>5.5×10^-10</td>
<td>0.61±0.04</td>
<td>0.40±0.03</td>
<td>8</td>
</tr>
<tr>
<td>SHR</td>
<td>7.6×10^-10</td>
<td>0.64±0.03</td>
<td>0.40±0.02</td>
<td>11</td>
</tr>
<tr>
<td>12-week-old</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>1.9×10^-9</td>
<td>0.73±0.02</td>
<td>0.46±0.02</td>
<td>14</td>
</tr>
<tr>
<td>SHR</td>
<td>1.0×10^-9</td>
<td>0.70±0.02</td>
<td>0.44±0.02</td>
<td>14</td>
</tr>
</tbody>
</table>

Values under Max and K' Max show mean±SEM. CI, 95% confidence interval; Max, maximum response to endothelin; K' Max, maximum response to K' depolarization (K'=50 mM); n, number of experiments; WKY, Wistar-Kyoto rats; SHR, spontaneously hypertensive rats.

*p<0.05 from age-matched WKY rats (unpaired t test).

increase in blood pressure induced by norepinephrine, Ang II, and ET might be due to its specific effect on the voltage-dependent Ca²⁺ channels in the vascular smooth muscle, especially in arterioles, which are the most important region for the blood pressure responses. However, the contractile mechanisms of the small artery have to be elucidated to understand the precise cellular mechanisms for the maintenance of blood pressure in general and excellent depressor effects and the antagonizing action of Ca²⁺ channel blockers against various agonists in particular.

As anticipated, a bolus injection of Ang II produced a potent pressor response comparable with that of ET. However, considering that the duration of the response to Ang II was much shorter than that to ET, it would be estimated that ET is a more intense pressor agent than Ang II. The time course of the pressor response to Ang II was similar to that of the rapid phase of the pressor response to ET. Continuous infusion of saralasin, an Ang II antagonist, markedly attenuated the pressor response to Ang II but scarcely attenuated the response to ET. PGF₂α also has been shown to evoke an increase in blood pressure by a single intravenous injection.²⁴

In the present study, however, indomethacin pretreatment did not inhibit the ET-induced pressor response. Therefore, it is unlikely that the pressor action of ET is mediated by the Ang II and PG systems. The results suggest that ET is a novel endogenous pressor substance and that the ET-induced pressor response was somewhat enhanced by indomethacin. De Nucci et al²⁵ have demonstrated that ET releases PGI₂ in the perfused lung of guinea pigs. Therefore, it is conceivable that such vasodilator PGs are released by intravenous injection of ET, in which case the pressor response to ET may be underestimated.

SHR displayed a similar pressor response as WKY rats did to ET. However, because the blood pressure before the injection of ET was higher in SHR than in WKY rats (After blockers in Table 2), the possibility remains that the response to ET in SHR may have been underestimated. The maximum response to the dose of 2,000 pmol/kg was significantly greater in 12-week-old SHR than in WKY rats. It has been reported that the ratio of media thickness to lumen diameter increases in blood pressure by a single intravenous injection.²⁴

TABLE 2. Characteristics of Rats Used in This Investigation

<table>
<thead>
<tr>
<th></th>
<th>6-week-old</th>
<th></th>
<th>12-week-old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP (mm Hg)</td>
<td>HR (beats/min)</td>
<td>BP (mm Hg)</td>
</tr>
<tr>
<td>Conscious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>112±5</td>
<td>421±30</td>
<td>138±3</td>
</tr>
<tr>
<td>SHR</td>
<td>124±5</td>
<td>420±20</td>
<td>175±4*</td>
</tr>
<tr>
<td>Anesthetized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>85±5</td>
<td>341±23</td>
<td>77±4</td>
</tr>
<tr>
<td>SHR</td>
<td>117±4*</td>
<td>384±7</td>
<td>103±4*</td>
</tr>
<tr>
<td>After blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>64±3</td>
<td>259±9</td>
<td>64±4</td>
</tr>
<tr>
<td>SHR</td>
<td>79±5*</td>
<td>262±8</td>
<td>75±2*</td>
</tr>
</tbody>
</table>

Each value is mean±SEM of six experiments. BP, blood pressure; HR, heart rate; Conscious, systolic arterial pressure and HR measured with a tail-cuff sphygomonanometer; WKY, Wistar-Kyoto rats; SHR, spontaneously hypertensive rats. Anesthetized, mean arterial pressure and HR measured from cannula in carotid artery with a pressure transducer under urethane anesthesia; After blockers, mean arterial pressure and HR after the treatment with atropine, propranolol, and bunazosin under urethane anesthesia.

*p<0.05 from age-matched WKY rats (unpaired t test).
12-week-old SHR,\textsuperscript{26,27} which probably augments the resistance to the large rise in blood pressure and may account for, at least in part, the enhanced maximum response to ET in SHR. This hypothesis is supported by the present result: no difference in the responsiveness was recognized between SHR and WKY rats of prehypertensive age (6 weeks) in which the media thickness is the same.\textsuperscript{27}

ET caused a potent dose-dependent vasoconstriction of the isolated mesenteric artery. The characteristics of the ET-induced contraction were slowly developing, long lasting, and poor recovering, which are common with those observed in the porcine coronary artery\textsuperscript{14} and the rat renal artery.\textsuperscript{15} Interestingly, the maximum tension induced by ET was greater than that of KCl-induced contraction. In the porcine coronary artery, the maximum effect of ET has been reported to be almost identical to that of K\textsuperscript{+} depolarization,\textsuperscript{14} which supports the hypothesis that the action of ET is related to a voltage-dependent Ca\textsuperscript{2+} channel. It would be reasonable to speculate, therefore, that ET causes the vasoconstriction of the rat mesenteric artery via a mechanism that is at least partly different from that of the porcine coronary artery. It is of no doubt that the mesenteric artery largely contributes to the systemic blood pressure as the resistance vessel. Regarding the reactivity of the mesenteric artery to ET in vitro, the present result showed that the vasocontractile effect of ET was more sensitive in 12-week-old SHR than in WKY rats. It has also been reported that vasocontractile sensitivity to ET is increased in the renal artery isolated from SHR.\textsuperscript{15}

The mechanisms of increased vasocontractile sensitivity to ET in the hypertensive stage are now under investigation in our laboratory.

It is not clear why this elevated vascular reactivity to ET does not result in the higher sensitivity in the pressor response to ET in SHR. One interpretation is that the elevated vasoactivity to ET was overcome by the other effects of ET. Fukuda et al\textsuperscript{28} have demonstrated that ET stimulates the secretion of the immunoreactive atrial natriuretic peptide. ET has also been found to induce the release of EDRF and PGI\textsubscript{2} in the isolated and perfused rat mesentery and isolated guinea pig lungs, respectively.\textsuperscript{25} In addition, it has also been reported that ET inhibits renin release in the isolated rat glomerular preparations.\textsuperscript{29} Besides the direct vasoconstrictive effect, which is the essential cause of the rise in the blood pressure, ET may have indirect suppressing effects on the blood pressure through acceleration or suppression of the release of such endogenous substances. Such complex action of ET in vivo might result in the blunted reactivity in SHR.

It is also possible that the inactivation mechanism of ET might be accelerated in SHR, such as the acceleration of the norepinephrine uptake into the nerve terminals of blood vessels in SHR.\textsuperscript{30} It has been reported that distinct morphological changes in endothelium do develop in hypertensive animals.\textsuperscript{31}

Considering that ET is released in large quantities under culture conditions that are perceived as abnormal situations for endothelial cells,\textsuperscript{14} an excessive production of ET may be brought about by the abnormality of the endothelium in SHR. This may in turn cause acceleration of the inactivation mechanism of ET. Further experiments are necessary to elucidate the production and inactivation mechanisms of ET and their contribution to the blunted reactivity in vivo to ET in SHR.

A bolus injection of ET induced a long-lasting pressor response that was highly sensitive to nicardipine, a dihydropyridine Ca\textsuperscript{2+} channel blocker currently used as an antihypertensive agent. The vasocontractile sensitivity to ET was increased in isolated arteries from SHR in the hypertensive stage, but the difference in pressor responses between SHR and WKY rats (12-week-old) was small. The reason for this discrepancy is obscure at present, and it appears to be unlikely that ET plays a central role in causing hypertension in this model. However, the possibility still remains that ET is an endogenous factor responsible for the maintenance of hypertension, although the exact role of ET released into the interstitial fluid has yet to be elucidated.

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KEY WORDS • angiotensin II • blood pressure • heart rate • mesenteric artery • vasoconstriction
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