Prevention of endothelin-1-induced increases in blood pressure: role of endogenous CGRP

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Wang, Youping, and Donna H. Wang. Prevention of endothelin-1-induced increases in blood pressure: role of endogenous CGRP. Am J Physiol Heart Circ Physiol 287:H1868–H1874, 2004. First published June 17, 2004; 10.1152/ajpheart.00241.2004—To determine the role of endothelin-1 (ET-1) and its receptors in the regulation of calcitonin gene-related peptide (CGRP) release, male Wistar rats were divided into six groups and subjected to the following treatments for 1 wk with or without ABT-627 (an ETA receptor antagonist, 5 mg·kg⁻¹·day⁻¹ in drinking water) or A-192621 (an ETα-receptor antagonist, 1 mg/kg) increased MAP (P < 0.05) in ET-1 (5 ng·kg⁻¹·min⁻¹ iv), Con + ABT-627, Con + A-192621, ET-1 + ABT-627, and ET-1 + A-192621. Baseline mean arterial pressure (MAP, mmHg) was higher (P < 0.05) in Con + A-192621 (122 ± 4) and ET-1 + A-192621 (119 ± 4) groups compared with Con (104 ± 6), ET1 (106 ± 3), Con + ABT-627 (104 ± 3), and ET1 + ABT-627 (100 ± 3) groups. Intravenous administration of CGRP (8–37) (a CGRP receptor antagonist, 1 mg/kg) increased MAP (P < 0.05) in ET-1 (13 ± 1), Con + A-192621 (12 ± 1), and ET-1 + A-192621 (15 ± 3) groups compared with Con (4 ± 1), Con-ABT-627 (4 ± 1), and ET-1 + ABT-627 (5 ± 1) groups. Plasma CGRP levels (in pg/ml) were increased (P < 0.05) in ET-1 (57.5 ± 6.1), Con + A-192621 (53.9 ± 3.4), and ET-1 + A-192621 (60.4 ± 3.0) groups compared with Con (40.4 ± 1.6), Con + ABT-627 (40.0 ± 2.9), and ET-1 + ABT-627 (42.6 ± 1.9) groups. Plasma ET-1 levels (in pg/ml) were higher (P < 0.05) in ET-1 (2.8 ± 0.2), ET-1 + ABT-627 (3.2 ± 0.4), Con + A-192621 (3.3 ± 0.4), and ET-1 + A-192621 (4.6 ± 0.3) groups compared with Con (1.1 ± 0.2) and Con-ABT-627 (1.3 ± 0.2) groups. Therefore, our data show that ET-1 infusion leads to increased CGRP release via activation of the ETα receptor, which plays a compensatory role in preventing ET-1-induced elevation in blood pressure.

endothelin receptor; calcitonin gene-related peptide

CALCITONIN GENE-RELATED PEPTIDE (CGRP) is a 37-amino acid vasoactive neuropeptide resulting from tissue-specific alternative splicing of the primary transcript of the calcitonin-calcitonin-gene-related peptide (CGRP) gene (30). Within the sensory nervous system, CGRP immunoreactivity has been detected prominently in dorsal root ganglia (DRG), which contain the cell bodies of sensory afferents (30). Immunohistochemical studies (30) have also found an abundance of CGRP-containing sensory nerve terminals throughout the body, often associated with vascular smooth muscle. Whereas many biological actions, including the regulation of nociception have been attributed to CGRP, it has been generally accepted that CGRP is one of the most potent endogenous vasodilators. Evidence shows that CGRP plays a vital role in regulating peripheral vascular tone and regional blood flow under both physiological and pathophysiological conditions (3, 27, 30).

Endothelin-1 (ET-1) is a potent vasoconstrictor peptide of 21 amino acids that is synthesized and released by endothelial cells (33). ET-1 activates two subtypes of receptors, endothelin-A (ETα) and endothelin-B (ETβ) receptors (9). ETα receptors are present in vascular smooth muscle cells and mediate endothelin-induced vasoconstriction (9). ETβ receptors are expressed predominately in endothelial cells and mediate vasodilation by generation of prostacyclin and nitric oxide (5, 10). Moreover, there is evidence showing that ETβ receptors bind and remove ET-1 from the circulation and thus serve as clearance receptors that minimize ETα receptor activation (9). Whereas ET-1 plays an important role via its autocrine and paracrine actions, it has been shown that its spillover into the blood stream under pathophysiological conditions associated with endothelial dysfunction elevates circulating ET-1 levels by two- to fivefold (4, 14).

Previous studies have demonstrated that in deoxycorticosterone acetate (DOCA)-salt hypertension, CGRP acts as a compensatory depressor to attenuate the elevation of blood pressure (27). The mechanisms responsible for the action appear to be through an increase in neuronal synthesis and subsequent release of CGRP in this model (27). These studies suggest that altered circulating and/or local factors in DOCA-salt hypertension may change the long-term synthesis and release of CGRP from sensory afferents. It has been shown that DOCA-salt hypertension is associated with an upregulation of the endothelin system (9). It is unknown, however, whether ET-1 plays a role in CGRP synthesis and release. The purpose of this study was, therefore, to determine the chronic action of ET-1 on CGRP release through intravenous administration of this peptide at 5 ng·kg⁻¹·min⁻¹. Our preliminary studies indicate that this dose of ET-1 elevates plasma ET-1 levels by twofold, a condition that mimics certain pathophysiological states (4, 14). In addition, the use of specific ETα and ETβ receptor antagonists allowed us to evaluate which receptor subtype is primarily responsible for the ET-1 action.

METHODS

Animal groups. All experiments were approved by the Institutional Animal Care and Use Committee. Male Wistar rats weighing 220–270 g (Charles River Laboratories; Wilmington, MA) were housed in the animal facility for 1 wk before the experiment and were allowed free access to regular rat chow throughout the experiment. All rats were divided into six groups and subjected to the following treatments for 1 wk: control (Con), ET-1, control + ABT-627 [2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-di(n-butyl)amino carbonyl]methyl]-pyrrolidine-3-carboxylic acid] (Con + ABT-627), control + A-192621 [2-(4-propanoylphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,5-eth-
Briefly, mesenteric arteries taken from control rats were fixed with Zamboni’s fixative solution for 3–6 h at 4°C. The arteries were then incubated with polyclonal sheep anti-ET_A (1:200, Alexis Biochemicals) for 12 h at room temperature, followed by overnight incubation with rabbit anti-rat CGRP antiserum (1:400, Sigma) at room temperature. Subsequently, the vessels were incubated in a mixture of biotin-conjugated anti-sheep IgG (1:500, Jackson ImmunoResearch) and Cy3-conjugated anti-rabbit IgG (1:300, Jackson ImmunoResearch) for 2 h at room temperature. Finally, the vessels were incubated with FITC-conjugated streptavidin (1:500, Jackson ImmunoResearch) for 45 min at room temperature. For double labeling of CGRP and protein gene product 9.5 (PGP9.5, a general neuronal marker) (29), mesenteric arteries were incubated sequentially with 1) rabbit anti-rat CGRP antiserum (1:400, Sigma) for 12 h at 4°C and 2) monoclonal mouse antibody to PGP9.5 (1:500, Biogenes) for 12 h at 4°C. Subsequently, the vessels were incubated with the secondary antibody as described above except that biotin-conjugated anti-sheep IgG was replaced by biotin-conjugated anti-mouse IgG (1:500, Jackson ImmunoResearch). The slides were viewed under a Zeiss Pascal confocal laser scanning microscope using 488-nm and 543-nm laser. Negative control for possible cross-reactivity between the fluorescent reagents was done by incubating the vessels with only one of the primary antibodies, followed by incubation with a mixture of the secondary antibodies. No cross-reactivity was observed.

Statistical analysis. All values are expressed as means ± SE. The differences among groups were analyzed using one-way ANOVA followed by a Bonferroni’s adjustment for multiple comparisons. Comparisons of systolic blood pressure before and after treatment were performed by using two-way ANOVA for repeated measurement with the Newmann-Keuls test. Comparisons of MAP before and after administration of CGRP8–37 were performed by using a paired t-test. Differences were considered statistically significant at P < 0.05.

RESULTS

After 1 wk of treatment, systemic blood pressure was significantly increased in the Con + A-192612 (130 ± 4 mmHg) and ET-1 + A-192621 (128 ± 3 mmHg) groups compared with Con (112 ± 1 mmHg), ET-1 (113 ± 3 mmHg), Con + ABT-627 (111 ± 2 mmHg), and ET-1 + ABT-627 (110 ± 3 mmHg) (P < 0.05) groups. MAP obtained from direct intra-arterial measurement was consistent with the systolic blood pressure (baseline MAP in Table 1 and Fig. 1). Therefore, neither systolic blood pressure nor MAP was elevated by ET-1 infusion. However, daily oral administration of the ET_A antagonist A-192621 increased systolic blood pressure and MAP in both control and ET-1-infused rats. In contrast, the ET_A antagonist ABT-627 did not alter systolic blood pressure or MAP in either control or ET-1-infused rats (Fig. 1).

To determine whether endogenous CGRP plays a compensatory role in preventing the ET-1-induced increase in blood pressure, MAP and heart rate (HR) responses to bolus injection of CGRP8–37 (1 mg/kg in 200–300 μl of normal saline) were examined under the fully awake and unrestrained state of rats. The MAP elevation began ~15–20 s after administration of CGRP8–37 and reached the peak 40–60 s after administration. The pressor activity of CGRP8–37 lasted for ~120 s. The baseline and maximal changes of MAP and HR and the differences between the baseline and maximal changes are listed in Table 1. CGRP8–37 infusion led to a significant increase in MAP in rats receiving ET-1 compared with the control group (Fig. 2 and Table 1). Moreover, the pressor...
Con (40.4 ± 11006 and ET-1 ± 11001 ET-1

Effect of intravenous administration of CGRP 8–37 on MAP and HR in conscious rats

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>MAP, mmHg (Baseline)</th>
<th>MAP, mmHg (After CGRP 8–37)</th>
<th>Δ MAP, mmHg</th>
<th>HR, beats/min (Baseline)</th>
<th>HR, beats/min (After CGRP 8–37)</th>
<th>Δ HR, beats/min</th>
</tr>
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<tbody>
<tr>
<td>Con</td>
<td>104 ± 6</td>
<td>108 ± 5</td>
<td>4 ± 1</td>
<td>383 ± 6</td>
<td>380 ± 5</td>
<td>–4 ± 2</td>
</tr>
<tr>
<td>Con + ABT-627</td>
<td>104 ± 3</td>
<td>108 ± 4</td>
<td>4 ± 1</td>
<td>388 ± 13</td>
<td>387 ± 14</td>
<td>–2 ± 3</td>
</tr>
<tr>
<td>Con + A-192621</td>
<td>122 ± 4*</td>
<td>134 ± 5†</td>
<td>12 ± 1*</td>
<td>382 ± 12</td>
<td>371 ± 11†</td>
<td>–11 ± 4</td>
</tr>
<tr>
<td>ET-1</td>
<td>106 ± 3</td>
<td>119 ± 3†</td>
<td>13 ± 1*</td>
<td>385 ± 9</td>
<td>374 ± 10†</td>
<td>–12 ± 1</td>
</tr>
<tr>
<td>ET-1 + ABT-627</td>
<td>100 ± 3</td>
<td>105 ± 3</td>
<td>5 ± 1</td>
<td>390 ± 10</td>
<td>387 ± 10</td>
<td>–3 ± 2</td>
</tr>
<tr>
<td>ET-1 + A-192621</td>
<td>119 ± 4*</td>
<td>133 ± 6†</td>
<td>15 ± 3*</td>
<td>378 ± 12</td>
<td>368 ± 11†</td>
<td>–10 ± 4</td>
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Values are means ± SE; n = 7–8 rats. CGRP, calcitonin gene-related peptide; Δ, difference between the peak value and baseline; ET-1, endothelin-1. Mean arterial pressure (MAP) and heart rate (HR) were measured by direct intra-arterial recording on day 7 of drug treatment in rats fully awake and unrestrained. Values for MAP and HR responses to calcitonin gene-related peptide antagonist (CGRP8–37) represent maximal changes or peak values (after CGRP8–37).

*P < 0.05 vs. the control group (Con), †P < 0.05 vs. baseline.

response induced by CGRP8–37 was observed in rats receiving the ETB antagonist with or without ET-1 but not in rats treated with the ETA antagonist (Fig. 2 and Table 1).

Plasma CGRP concentrations in each of the six groups were shown in Fig. 3. Plasma CGRP levels were increased in ET-1 (57.5 ± 6.1 pg/ml), Con + A-192621 (53.9 ± 3.4 pg/ml), and ET-1 + A-192621 (60.4 ± 3.0 pg/ml) groups compared with Con (40.4 ± 1.6 pg/ml), Con + ABT-627 (40.0 ± 2.9 pg/ml), and ET-1 + ABT-627 (42.6 ± 1.9 pg/ml) groups (P < 0.05).

Therefore, circulating CGRP was significantly increased in response to ET-1 infusion. Plasma CGRP concentration was also significantly higher in rats receiving the ETB antagonist with or without ET-1 infusion. In contrast, no significant difference in DRG CGRP content was observed among groups (Fig. 3).

Plasma ET-1 levels were higher in ET-1 (2.8 ± 0.2 pg/ml), ET-1 + ABT-627 (3.2 ± 0.4 pg/ml), Con + A-192621 (3.3 ± 0.4 pg/ml), and ET-1 + A-192621 (4.6 ± 0.3 pg/ml) groups compared with Con (1.1 ± 0.2 pg/ml) and Con-ABT-627 (1.3 ± 0.2 pg/ml) groups (Fig. 4, P < 0.05). Therefore, plasma ET-1 concentrations were increased in rats receiving the ETB antagonist alone or in rats infused with ET-1 with or without receiving the ETA antagonist. Coadministration of ET-1 plus the ETB antagonist resulted in a further increase in plasma ET-1 concentration compared with rats receiving ET-1 infusion alone.

Double staining of the ETA receptor and the marker of primary afferent fibers CGRP revealed that ETA receptors were present in perivascular sensory nerve fibers and colocalized with CGRP (Fig. 5). All CGRP-positive sensory fibers appeared to express ETA receptors.

As expected, these CGRP-positive sensory fibers consisted of only a subpopulation of the total perivascular nerve fibers, which were visualized by PGP9.5 (a general neuronal marker) (Fig. 5).
DISCUSSION

The present study provides new findings regarding the role of ET-1 in the regulation of CGRP release in the rat. Our results showed that blockade of the CGRP receptor by CGRP8–37 leads to an increase in blood pressure in chronically ET-1 infused rats, suggesting that ET-1 infusion leads to an increase in CGRP release, which plays a compensatory role in preventing ET-1-induced elevation in blood pressure. Indeed, we found that the plasma CGRP level, determined by radioimmunoassay, is increased during chronic ET-1 infusion. Furthermore, our data demonstrate that acute pressor responses to CGRP8–37 and increased plasma CGRP levels in ET-1-treated rats are abolished by an ET A receptor antagonist but not an ET B receptor antagonist, indicating that ET-1 promotes CGRP release via activation of the ET A receptor.

CGRP acts as a vasodilator to directly dilate multiple vascular beds through endothelium-dependent or endothelium-independent mechanisms (8, 18). There are several potential mechanisms by which CGRP attenuates the increase in blood pressure. In the current study, one possibility is that the acute pressor responses to CGRP8–37 are derived from a direct interaction of the antagonist with peripheral vascular CGRP receptors. Alternatively, it is possible that CGRP8–37 increases blood pressure through enhancing sympathetic nerve activity. Accumulating evidence indicates that CGRP contributes to the regulation of cardiovascular function through inhibition of sympathetic nervous activity (19). It has been shown that the vasoconstriction response to adrenergic nerve stimulation is potentiated by capsaicin-induced denervation of sensory nerves and by CGRP8–37, suggesting that CGRP suppresses adrenergic nerve-induced vasoconstriction via both prejuncional and postjunctional mechanisms (22, 28).

Our data show that increased MAP response to CGRP8–37 in ET-1-treated rats is accompanied by an increase in the circulating level of CGRP but not CGRP content in DRG. This finding may be explained by the fact that ET-1 stimulates CGRP release rather than CGRP synthesis in sensory nerves. The fact that our data show colocalization of ETA and CGRP in the sensory nerve fibers supports the notion that ET-1-mediated CGRP release is mediated by activation of the ET A receptor. Indeed, Gokin et al. (7) reported that peripheral administration of ET-1 induces nocifensive behavior that is reversible by administration of an ET A receptor antagonist, suggesting that ET A receptors are present in sensory afferents. This view is further supported by Pomonis et al. (21) who reported that ET A receptor immunoreactivity is found in CGRP-containing sensory neurons in DRG, whereas ET B receptor immunoreactivity is seen in DRG satellite cells or Schwann cells.

We observed that infusion of ET-1 increased plasma ET-1 concentration approximately two- to threefold without changing baseline blood pressure. The results are consistent with previous studies by Mortensen and Fink (17). They reported that chronic ET-1 infusion at 5 pmol·kg⁻¹·min⁻¹ (≈12 ng·kg⁻¹·min⁻¹), a dose that was about two to three times higher than what has been used in the current study, did not cause an increase in blood pressure in rats fed a normal sodium diet.

Several observations show that CGRP is a potent vasodilator and natriuretic factor (30). It has been demonstrated that CGRP acts as a vasodilator to directly dilate multiple vascular beds through endothelium-dependent or endothelium-independent mechanisms (8, 18). There are several potential mechanisms by which CGRP attenuates the increase in blood pressure. In the current study, one possibility is that the acute pressor responses to CGRP8–37 are derived from a direct interaction of the antagonist with peripheral vascular CGRP receptors. Alternatively, it is possible that CGRP8–37 increases blood pressure through enhancing sympathetic nerve activity. Accumulating evidence indicates that CGRP contributes to the regulation of cardiovascular function through inhibition of sympathetic nervous activity (19). It has been shown that the vasoconstriction response to adrenergic nerve stimulation is potentiated by capsaicin-induced denervation of sensory nerves and by CGRP8–37, suggesting that CGRP suppresses adrenergic nerve-induced vasoconstriction via both prejuncional and postjunctional mechanisms (22, 28).

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diet (2 meq/day). The blood pressure increased in these rats only when a high-salt diet was given (17). Therefore, despite the fact that ET-1 is a potent vasoconstrictor and prohypertensive factor, ET-1-mediated blood pressure regulation appears to be the result of the balance between ETA-mediated vasoconstriction, ET A-stimulated increases in CGRP release and vasodilation, and ET B-mediated vasodilation.

Indeed, several studies (6, 15) have shown that selective or nonselective ET B receptor antagonists increase plasma ET-1. This increase may be due to displacement of ET-1 from receptors into the circulation (15) and/or an antagonism of an ET-1 clearance pathway (6). In the current study, blood pressure increased when ET B receptors were blocked even in rats without receiving ET-1 infusion. This pressor response to ET B blockade may be due to impaired release of endothelial vasodilators (nitric oxide and prostacyclin) and/or increased ET A receptor stimulation via, at least in part, diminished ET-1 clearance (9). Interestingly, the elevation of systolic blood pressure reached a plateau after 4 days of treatment with the ET B antagonist. It is possible that the window of the tail-cuff measurement in this study was not long enough to show further elevation of blood pressure or that additional environmental stress such as high-salt intake would be needed to increase blood pressure further.

It is noted that, whereas plasma CGRP levels were not different between rats treated with ET-1 alone and rats treated with the ET B antagonist with or without ET-1, MAP was higher only in the latter two groups of rats. This raises the question as to, if CGRP played a role in ET-1-mediated blood pressure regulation, why was the blood pressure not at the same level in these three groups of rats? Although the mechanism(s) responsible for this phenomenon is unknown, the following possibilities exist. One is that increased plasma CGRP levels were insufficient in counteracting ET A-mediated

Fig. 5. Confocal microscope images of double-immunofluorescence staining of mesenteric small and resistance arteries (A–I). A and D: FITC-labeled ET A receptor staining (green). B, E, and H: Cy3-labeled calcitonin gene-related peptide (CGRP) staining (red). C and F: colocalization of ET A and CGRP (yellow). G: FITC-labeled PGP9.5 staining (green). I: colocalization of PGP9.5 and CGRP (yellow). A–I, and D–F, and G–I represent the same single segment of the mesenteric arteries, respectively. Scale bars, 100 μm.
vasoconstriction without the participation of \( \text{ET}_B \) as shown in the case in which rats were treated with the \( \text{ET}_B \) antagonist with or without \( \text{ET}_1 \). Another possibility would be that intact \( \text{ET}_B \) receptor function is obligatory for CGRP to play a compensatory effect on preventing \( \text{ET}_1 \)-induced increase in blood pressure as shown in the case in which rats were treated with \( \text{ET}_1 \) alone.

Although the molecular mechanisms by which \( \text{ET}_1 \) stimulates CGRP release from sensory afferents are largely unknown, several lines of evidence support the hypothesis that \( \text{ET}_1 \) may exert its actions via protein kinase C (PKC) and/or prostaglandins pathways. It has been shown that \( \text{ET}_1 \) activates PKC via the \( \text{ET}_A \) receptor in cardiac myocyte, as well as in other tissues (25, 32). Also, studies have shown that activators of PKC upregulate CGRP and calcitonin synthesis and release in primary cultures of nodose sensory ganglia and medullary thyroid carcinoma cell lines (2, 16). Alternatively, Wright and Malik (31) demonstrated that activation of the \( \text{ET}_A \) receptor promotes prostacyclin synthesis in vascular smooth muscle through a PKC-independent mechanism. It is well established that prostacyclin directly stimulates CGRP release from sensory neurons or sensitizes the sensory neuron responses to other stimuli (11). These findings support the notion that prostacyclin produced by activation of the \( \text{ET}_A \) receptor evokes or potentiates CGRP release.

**Perspectives.** The present study shows that a sensory neurotransmitter CGRP may participate in blood pressure regulation in \( \text{ET}_1 \)-treated rats via an \( \text{ET}_A \)-dependent mechanism. It is well documented that the endothelin system is activated in certain forms of salt-sensitive hypertension in both humans and animals (12, 23). Moreover, there is accumulating evidence showing that a defect in the sensory nerve system exists in spontaneously hypertensive rats and Dahl-salt hypertensive rats (13, 26). It is conceivable that sensory nerve dysfunction may contribute to the development of hypertension in these models of hypertension. Given the fact that endogenous CGRP may act as a mediator to buffer the elevation of blood pressure, it is reasonable to speculate that agents that modulate the sensory nerve or selectively enhance the sensory nerve activity in advanced atherosclerosis, N Engl J Med 325: 997–1001, 1991.

**Perspectives.** The present study shows that a sensory neurotransmitter CGRP may participate in blood pressure regulation in ET1-treated rats via an ETA-dependent mechanism. It is well documented that the endothelin system is activated in certain forms of salt-sensitive hypertension in both humans and animals (12, 23). Moreover, there is accumulating evidence showing that a defect in the sensory nerve system exists in spontaneously hypertensive rats and Dahl-salt hypertensive rats (13, 26). It is conceivable that sensory nerve dysfunction may contribute to the development of hypertension in these models of hypertension. Given the fact that endogenous CGRP may act as a mediator to buffer the elevation of blood pressure, it is reasonable to speculate that agents that modulate the sensory nerve system may be beneficial in treating hypertension as well as in reducing the long-term complications resulting from hypertension.

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