Endothelin-1 Regulates Tone of Isolated Small Arteries in the Rat  
Effect of Hyperendothelinemia

Eric Thorin, Peter Cernacek, Jocelyn Dupuis

Abstract—Chronic elevation of plasma endothelin-1 (ET-1) levels has been reported in several pathological conditions. To investigate the consequences of increased circulating ET-1 on vascular responsiveness, Sprague-Dawley rats (n = 16) were chronically instrumented with a minipump delivering ET-1 at a constant dose for 7 days. Plasma ET-1 levels were more than doubled in treated (0.98 ± 0.09 pmol/L; P < .05) versus untreated sham-operated rats (0.43 ± 0.04 pmol/L), whereas systolic arterial blood pressure increased (139 ± 5 versus 128 ± 4 mm Hg in untreated rats; P < .05). After rats were killed, segments of middle cerebral (MCA) and mesenteric (MES) arteries were mounted on an isometric myograph. ET-induced contraction was shifted to the right in ET-1–treated animals and not modified by BQ123 (an ET A receptor antagonist); bosentan (ET A/B receptor antagonist) prevented ET-1–induced contraction in both groups. After inhibition of nitric oxide synthase with \( N^\circ \)-nitro-L-arginine (L-NNA), both phenylephrine and oxymetazoline (an \( \alpha_2 \)-adrenoceptor agonist) induced MCA contraction. The sensitivity to phenylephrine was decreased in ET-1–treated compared with control rats (P < .05). Sensitivity to phenylephrine-induced contraction was decreased by BQ123 in control rats only. In contrast, L-NNA revealed greater oxymetazoline-induced contractions in treated compared with control MCA rings (P < .05); this potentiation was blunted by bosentan but unaffected by BQ123. Removal of the endothelium revealed a direct constrictor effect of oxymetazoline that was insensitive to L-NNA alone or combined with bosentan; however, oxymetazoline induced significantly lower constriction in treated rat MCA segments. Responses to oxymetazoline were also blunted in treated compared with untreated denuded MES arteries. In conclusion, chronic elevated plasma ET-1 decreases smooth muscle cell sensitivity to contractile agonists both in MCA and MES rings. In cerebral vessels, endothelial \( \alpha_2 \)-adrenoceptor–dependent stimulation induced greater contractile responses in treated rats which were sensitive to bosentan, suggesting that oxymetazoline stimulates ET-1 release from the endothelium. This may represent a compensatory mechanism for the loss of smooth muscle sensitivity. (Hypertension. 1998;31:1035-1041.)

Key Words: mesenteric arteries n cerebral arteries n adrenergic antagonists n endothelin n rats

Increased circulating ET-1 levels have been reported in various pathological conditions such as hemorrhagic stroke,\(^1\,^2\) atherosclerosis,\(^3\) diabetes,\(^4\) obesity,\(^5\) myocardial infarction,\(^6\) and congestive heart failure.\(^7\) Patients with these conditions demonstrated a twofold to threefold increase in ET-1 levels. The origin of this increase remains to be elucidated, although in atherosclerotic patients, ET-1 seems to originate from the vascular lesion.\(^3\,^9\) The short-term increase in circulating ET-1 levels was shown to be closely associated with the appearance of cerebral vasospasm\(^2\) and pharmacologically induced coronary vasospasm in patients with variant angina pectoris.\(^10\) On the basis of data from acute ET-1 infusion in anesthetized dogs, Lerman and coworkers\(^11\) suggested that a twofold increase in circulating levels of ET-1 may be sufficient to locally reach a threshold that could facilitate the appearance of coronary spasm. Similarly, Yang and coworkers\(^12\) concluded that subthreshold concentration of ET-1 could facilitate the appearance of human vascular spasm on the basis of in vitro experiments. It has also been shown that low ET-1 levels (0.1 nmol/L) inhibited substance P–induced, and to a lesser extent acetylcholine-induced, dilation in dog MCAs, which could facilitate constriction.\(^13\) However, these experiments were performed acutely, mimicking more closely the consequences of a hemorrhagic stroke than conditions of severe atherosclerosis, where circulating levels of ET-1 are elevated for several months. Conceivably, long-term exposure to ET-1 may modify vascular reactivity by influencing ET-1 production and receptor expression and/or sensitivity, as well as smooth muscle cell sensitivity.
The objective of this study was to investigate the effect of increased levels of circulating ET-1 on the reactivity of isolated rat small arteries. Four questions were asked: (1) Does a chronic elevated ET-1 modify vascular responsiveness to exogenous ET-1? (2) Is the observed change in contractility selective for exogenous ET-1 or does it affect other contractile agonist responsiveness? (3) Are those changes in responsiveness to contractile agonists attributable to smooth muscle cells and/or endothelial cells? (4) Does chronic elevation of plasma ET-1 levels affect vascular beds differently? To achieve our goals, we used minipumps for continuous delivery of ET-1, thereby doubling basal circulating ET-1 levels. Our results show that circulating ET-1 decreases smooth muscle cell sensitivity to exogenous ET-1 and the α-adrenergic agonists in both cerebral and mesenteric vessels. However, ET-1 treatment increases endothelium-dependent constricting responses to OXY, a selective α₁-adrenergic agonist, in cerebral arteries.

**Methods**

**Minipump Implantation**

Sprague-Dawley rats (250 to 300 g) were housed under diurnal lighting conditions and allowed food and tap water ad libitum. At day 0, rats were anesthetized with halothane, and the jugular vein was exposed. A silicon catheter connected to the minipump (Alzet) was inserted into the treated rats only. The minipump was filled with 230 μL of a saline solution containing 21 μg of ET-1 (38 μmol/L). The solution was delivered in the venous bloodstream at a rate of 1.6 pmol · kg⁻¹ · min⁻¹. At day 7, systolic arterial pressure was recorded in the awake animals by the tail-cuff method. Rats were then anesthetized, and 2 mL of blood was rapidly withdrawn from the jugular vein. A silicon catheter connected to the minipump (Alzet) was inserted into the treated rats only. The minipump was filled with 230 μL of a saline solution containing 21 μg of ET-1 (38 μmol/L). The solution was delivered in the venous bloodstream at a rate of 1.6 pmol · kg⁻¹ · min⁻¹. At day 7, systolic arterial pressure was recorded in the awake animals by the tail-cuff method. Rats were then anesthetized, and 2 mL of blood was rapidly withdrawn from the aorta for ET-1 quantification.

**Isometric Recording of Tension of Isolated Microvessels**

Rat MCA and MES (third-order branches) arteries were harvested from halothane-anesthetized rats and placed in ice-cold PSS containing indomethacin (10 μmol/L), inhibitor of cyclooxygenase) and of the following composition (mmol/L): NaCl 130, KCl 4.7, KH₂PO₄ 1.18, MgSO₄ 1.17, NaHCO₃ 14.9, EDTA 0.026, glucose 10, and aerated with 12% O₂/5% CO₂/83% N₂ (pH 7.4). Segments of 2 mm in length were mounted on 20-μm tungsten wires in microvessel myographs (IMF, University of Vermont) as previously described. After a 1-hour stabilization period, arterial segments were challenged with 40 mmol/L KCl PSS; after one 15-minute washout period, vessels were stretched again and rechallenged with 40 mmol/L KCl PSS. This sequence was repeated until a stable contractile response was reached (usually between two to three challenges). The resulting baseline optimal tension was similar in control and treated rat arterial segments (data not shown). The endothelium was removed mechanically by gentle rubbing with a human hair. The effectiveness of endothelium removal was confirmed by the absence of dilatation to acetylcholine (1 μmol/L) in arteries preconstricted with serotonin (10 μmol/L) or 40 mmol/L KCl PSS. To prepare K⁺-rich solutions, equimolar amounts of NaCl were replaced with KCl.

The EC₅₀ of agonists was measured from each individual dose-response curve using a logistic curve-fitting program. The pD₂ value is the negative log of the EC₅₀ of agonists.

**ET-1 Measurements**

Plasma ET-1 levels were measured using a standard RIA method. Briefly, plasma was added to an activated Sep-Pak C₁₈ column (Waters), and the column was washed with 10 mL of water; ET-1 was eluted with 100% methanol (3 mL). All samples were desiccated in a Speedvac and resuspended in 500 μL of RIA buffer (pH 7.4) of the following composition (mmol/L): NaH₂PO₄ 19, Na₂HPO₄ 81, NaCl 50, and 0.01% sodium azide, 0.1% albumin, and 0.1% Triton X. The RIA procedure was performed according to the procedure described by the ET-1 antibody supplier (Peninsula).

Proteins were determined using fluorescamine as previously described. The drugs used were acetylcholine, indomethacin, L-NNA, OXY, PE (all from Sigma), ET-1, anti–ET-1 antibody (Peninsula), [¹²⁵I]ET-1 (Amersham), and BQ123 (American Peptide Company). Bosentan was a gift from Dr Martine Clozel (Hoffmann-La Roche Ltd, Basel, Switzerland). All drugs were dissolved in PSS except for indomethacin, which was dissolved in ethanol, and bosentan, which was dissolved in DMSO; final concentrations of ethanol or DMSO in the bath were 0.1% (vol/vol). Solutions were prepared fresh every day and kept on ice except for bosentan, which was kept at room temperature.

**Statistical Analysis**

Results are expressed as mean±SEM. In all experiments, n equals the number of rats. Vasorestrictions are expressed as percentage of Max indicates maximal response (%E_max). Results are expressed as mean±SEM; n=5 per group.

| TABLE 1. Effect of ET Treatment on pD₂ Values and Maximal Response to ET-1 in Isolated Rat MCAs in the Absence (Control) or Presence of BQ123 (1 μmol/L) |
|---|---|---|---|---|
| Untreated Rats | Treated Rats |
| Control | BQ123 | Control | BQ123 |
| pD₂ | 8.2±0.3 | 7.3±0.4* | 7.8±0.4 | 7.5±1.1 |
| Max | 82.7±3.3 | 87.9±3.4 | 84.5±3.8 | 85.1±6.4 |

*P<.05 vs control. Max indicates maximal response (%E_max). Results are expressed as mean±SEM; n=5 per group.
the maximal response (E_max) obtained in the presence of 127 mmol/L KCl PSS at the end of each individual experiment; vasorelaxations are expressed as the percentage of inhibition of the preconstricting tone. Statistical differences between means were determined by ANOVA followed by a Scheffe’s F test. In appropriate conditions, an tone. Statistical differences between means were determined by

Results

General Parameters
At day 7, the body weight of the treated rats (365 ± 6 g; n = 16) was increased compared with control sham-operated animals (331 ± 6 g; n = 16, P < .05). [ET-1]_a was significantly increased with treatment (0.98 ± 0.09 pmol/L) compared with control (0.43 ± 0.04 pmol/L; P < .05). Systolic arterial pressure was significantly higher in ET-1–treated animals (139 ± 5 mm Hg) compared with controls (128 ± 4 mm Hg; P < .05), whereas heart rate did not differ (392 ± 11 bpm in treated and control rats, respectively).

MCA rings had an external diameter of 198 ± 6 and 217 ± 7 µm in untreated and treated animals, respectively. MES segments had a diameter of 255 ± 6 and 244 ± 4 µm in untreated and treated animals, respectively.

Reactivity of Isolated MCA
ET-1 induced a potent vasoconstriction of isolated MCA rings (Fig 1). BQ123 (1 µmol/L) significantly shifted to the right (Table 1) the dose-response curve to ET-1 in untreated animals (Fig 1A) but had no effects in treated rats, suggesting a decrease in ET_A-dependent response (Fig 1B). ET-1 treatment did not alter the sensitivity and the maximal response to exogenous ET-1 (Table 1). Bosentan (10 µmol/L) abolished exogenous ET-1–dependent contraction except for the highest concentration tested (Fig 1).

To investigate whether the decrease in ET_A receptors induced by the treatment altered the responsiveness to other contractile agonists, we studied the effect of PE, a selective α_2-adrenergic agonist, to which responses are dependent on the activation of smooth muscle cells. PE induced a small but significant contractile response for concentrations >3 µmol/L in untreated animals (Fig 2A) but had no effect in treated rats (Fig 2B). In the presence of L-NNA (100 µmol/L), PE-mediated contraction was strongly potentiated in both groups. In the presence of BQ123 (1 µmol/L), the sensitivity to PE (Table 2) was decreased in control arterial rings only (Fig 2). Bosentan had no further effects in both groups.

To further study ET-1 treatment–induced reactivity changes, we studied the effect of OXY, a selective α_2-adrenergic agonist, responses to which are dependent on both activation of smooth muscle and endothelial cells receptors. OXY induced vasoconstriction only after inhibition of the

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### Table 2. Effect of ET Treatment on pD2 Values and Maximal Response to Agonists in Isolated Rat MCAs in the Absence (Control) or Presence of L-NNA (100 µmol/L) Alone or Combined With BQ123 (1 µmol/L) or Bosentan (10 µmol/L)

<table>
<thead>
<tr>
<th></th>
<th>Oxymetazoline</th>
<th>Phenylephrine</th>
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<td>With Endothelium</td>
<td>Without Endothelium</td>
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<tr>
<td></td>
<td>L-NNA</td>
<td>BQ123</td>
<td>BOS</td>
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<tr>
<td>Untreated rat MCA</td>
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<tr>
<td>pD2</td>
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<td>6.3±0.1</td>
<td>6.3±0.1</td>
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<tr>
<td>Max</td>
<td>19.2±1.5</td>
<td>17.4±1.8</td>
<td>18.7±3.5</td>
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<tr>
<td>Treated rat MCA</td>
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<tr>
<td>pD2</td>
<td>6.1±0.1</td>
<td>6.3±0.1</td>
<td>6.6±0.1*</td>
</tr>
<tr>
<td>Max</td>
<td>28.2±4.0</td>
<td>22.5±5.6</td>
<td>10.9±1.0*</td>
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Max indicates maximal response (%E_max). Results are expressed as mean±SEM; n = 5 to 8 per group.

*P<.05 vs L-NNA; †P<.05 vs with endothelium; ‡P<.05 vs untreated.
nitric oxide/L-arginine pathway (Fig 3). The contractile response was higher in treated compared with untreated animals without change in sensitivity (Table 2). ET-1 receptor antagonism did not influence $\alpha_2$-adrenergic responses in untreated animals, whereas in treated rats, bosentan but not BQ123 significantly decreased OXY-induced contraction and sensitivity (Fig 3B, Table 2).

OXY-induced contraction was present after endothelial denudation: responses were greater and the sensitivity decreased in control MCA (Fig 4, Table 2). Addition of L-NNA combined or not with bosentan had no effect on the response (Fig 4, Table 2), demonstrating that the effects of both drugs were endothelium dependent. Compared with control denuded MCA rings, ET-1 treatment reduced both the sensitivity to OXY and the amplitude of the contractile response (Fig 4, Table 2). Compared with intact ET-1–treated MCA rings, endothelial denudation significantly decreased the sensitivity to OXY without changing the maximal contractile response (Table 2).

Reactivity of Isolated MES
To study whether ET-1-treatment homogeneously affected the reactivity of various vascular beds, we investigated the effect of the treatment on isolated MES arteries of a diameter similar to that of the MCA. ET-1 induced a potent vasoconstriction of isolated MES artery segments (Fig 5). BQ123 (1 $\mu$mol/L) significantly shifted to the right (Table 3) of the dose-response curve to ET-1 in untreated animals (Fig 5A), but it had no effects in treated rats (Fig 5B). ET-1 treatment did not affect the maximal response and sensitivity to ET-1 added to the bath (Table 3). Bosentan (10 $\mu$mol/L) abolished all contractions mediated by exogenous ET-1 (Fig 5). The treatment therefore had similar effects in MES and MCA vessels.

However, neither PE nor OXY induced contraction of isolated MES artery segments in basal conditions or after inhibition of the nitric oxide/L-arginine pathway with L-NNA (data not shown).

After removal of the endothelium, OXY induced a potent contraction that was unaffected by subsequent addition of L-NNA and bosentan (Fig 6). Both the maximal response and the sensitivity to OXY were decreased in ET-treated rats compared with control (Fig 6, Table 4). The treatment therefore had similar effects in denuded MES and MCA vessels.

Discussion
The aim of this study was to investigate the role of ET-1 and the consequences of hyperendothelinemia on small-artery reactivity in rats. Two vascular beds were selected for this study, and contractile responses to selective $\alpha_1$- and $\alpha_2$-
adrenergic agonists and ET-1 were tested. Two important observations were made: first, constitutively released endothelium-derived ET-1 increases smooth muscle sensitivity to contractile agonists via activation of ET\(_A\) receptors; the importance of this mechanism decreases in ET-treated rats because of a decrease in sensitivity and/or number of smooth muscle ET\(_A\) receptors. Second, in ET-1–treated rats, \(\alpha_2\)-adrenergic receptor stimulation induces greater MCA constriction; this response appears to be dependent on the stimulated release of endothelium-derived ET-1.

**Plasma Concentration of ET**

The increase in [ET-1], has been reported in relation to several pathological conditions in humans.\(^{2-7}\) The origin of this increase remains uncertain and may vary depending on the pathology.\(^{16}\) However, the consequences of chronic elevated plasmatic ET-1 on vascular reactivity are not documented. In this study, we chose an ET-1 concentration to mimic pathophysiological levels. An increase of twofold to threefold in plasma ET-1 levels has been reported in most instances where ET-1 level increase has been reported\(^2\) and was successfully reproduced in our model. The elevated [ET-1]\(_0\) caused the rise in systolic arterial pressure (10 mm Hg) after 7 days in treated rats.

ET-1 treatment had an unexpected effect on weight: treated animals were 10% heavier than untreated rats. ET-1 has a known trophic effect that may increase the muscular mass of the animals.\(^{10}\) Furthermore, ET-1 induces insulin resistance in conscious rats that may modify glucose metabolism and increase fat storage.\(^{17}\) These mechanisms may have contributed to the observed increase in weight but remain speculative and deserve more attention in future studies.

**Vascular Reactivity to \(\alpha_2\)-Adrenergic Agonist and ET**

The physiological role of endogenous ET-1 in the cardiovascular system is not clearly defined. It has been reported that forearm blood flow increases in humans\(^{18}\) and dog cerebral arteries dilate\(^{19}\) after ET-1 receptor blockade. Our results demonstrate that the constitutive release of endothelium-derived ET-1 affects smooth muscle cell sensitivity in vitro and facilitates PE-induced contraction of isolated rat MCA; in the presence of BQ123 or bosentan, contractile responses to the \(\alpha_2\)-adrenergic receptor agonist were shifted to the right without change in maximum responses (Fig 2A, Table 2). This suggests that ET\(_A\) receptors are responsible for the sensitization of the underlying vascular smooth muscle to ET-1. The cellular mechanisms for smooth muscle sensitization are likely to involve both an ET-1–dependent increase in Ca\(^{2+}\) influx and Ca\(^{2+}\) sensitivity of contractile elements via a protein kinase C–dependent mechanism.\(^{20,21}\)

Contractions induced by exogenous ET-1 were also shifted to the right in the presence of the selective ET\(_A\) receptor antagonist without change in maximal response and were almost completely blocked by bosentan, a nonselective ET\(_A/B\) receptor antagonist. This suggests that ET\(_B\) receptors are responsible for ET-1–induced contraction in rat cerebral arteries. Similarly, ET-1–induced contraction of MES arteries was blocked by bosentan and only shifted to the right by BQ123 without change in maximal response. On the basis of these results, we propose that ET\(_A\) and ET\(_B\) receptors have two different physiological functions, with ET\(_A\) receptors being involved in smooth muscle cell sensitization to contractile agonists while ET\(_B\) receptors are responsible for contractile responses induced by ET-1.

**Vascular Reactivity to \(\alpha_2\)-Adrenergic Agonist**

The results obtained in the presence of OXY, a selective \(\alpha_2\)-adrenergic receptor agonist, seem not to support the hypothesis of constitutively released ET-1–induced sensitization of smooth muscle cell via activation of ET\(_A\) receptors; indeed, ET-1 receptor antagonism had no effect on the contractile response induced by OXY after nitric oxide formation blockade (Fig 3A). There is, however, a fundamental difference between \(\alpha_1\)- and \(\alpha_2\)-adrenergic receptors: whereas \(\alpha_1\)-adrenergic receptors are only expressed on smooth muscle cells, \(\alpha_2\)-adrenergic receptors are present both on smooth muscle and endothelial cells. Consequently, the vascular effect of OXY will represent combined endothelium- and smooth muscle–dependent responses. Activation of smooth muscle \(\alpha_2\)-adrenergic receptors triggers contraction, whereas endothelial \(\alpha_2\)-adrenergic receptor occupation usually mediates relaxation of preconstricted arteries in vitro.\(^{14,22-25}\)

The data obtained in treated rats, however, suggest that in the absence of preconstricting tone, activation of endothelial \(\alpha_2\)-adrenergic receptors mediates a contraction that is sensitive to bosentan but not BQ123. It seems therefore that \(\alpha_2\)-adrenergic receptors triggers the release of ET-1 that stimulates smooth muscle ET\(_A\) receptors. It remains to be clarified why this mechanism is effective in ET-treated rats only. It is possible that endothelial cells exposed to increased external concentration of ET-1 take up circulating ET-1. Most stimuli such as \(\alpha\)-thrombin,\(^{26}\) insulin,\(^{27}\) oxidized LDL,\(^{28}\) and hemodynamic shear stress\(^{29}\) regulate ET-1 release at the level of gene transcription. It has been reported, however, that preproendothelin-1 and ET-1 are stored in intracellular vesicles in cultured bovine aortic endothelial

| TABLE 4. Effect of ET Treatment on pD\(_2\) Values and Maximal Response to Agonists in Isolated and Denuded Rat MES Arteries in the Absence (Control) or Presence of L-NNA (100 \(\mu\)mol/L) Alone or Combined With BQ123 (1 \(\mu\)mol/L) |
|------------------|------------------|------------------|
|                  | Untreated Rats   | Treated Rats     |
|                  | Control | L-NNA | BOS  | Control | L-NNA | BOS  |
| pD\(_2\)          | 6.2±0.1 | 6.6±0.1 | 6.1±0.1 | 5.3±0.3* | 5.8±0.3* | 5.7±0.1* |
| Max              | 75.2±2.9 | 69.2±3.1 | 70.2±6.2 | 50.4±2.4* | 47.1±4.8* | 47.9±2.8* |

Max indicates maximal response (%E\(_{\text{max}}\)); BOS, bosentan. Results are expressed as mean±SEM; n=5 to 8 per group.

\(^*P<.05\) vs untreated.
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potent constrictions in denuded MES vessels, it is likely that in our experimental conditions, the endothelium exerts a potent inhibition on α-adrenergic, but not ET-1, contractile responses by a mechanism that remains to be elucidated. However, similar to the MCA, ET-1 treatment decreased smooth muscle sensitivity in denuded arteries. This demonstrates that hyperendothelinemia affects to a similar extent smooth muscle cells from cerebral and MES vessels. ETA receptors are also downregulated in MES arteries because BQ123 had no effect in treated vessels stimulated with exogenous ET-1 in vitro.

Pathophysiological Significance

The increase in extracellular ET-1 levels leads to a decrease in smooth muscle cell sensitivity. Agonists that act via smooth muscle activation have their response reduced, whereas α-adrenergic agonists, which have a dual action on endothelial and smooth muscle cells, have their responses exacerbated. It is tempting to favor the hypothesis that the endothelial component is most affected because blood pressure is increased in treated animals, therefore suggesting that endothelium-derived ET-1 overcompensates for the loss in smooth muscle cell sensitivity. We cannot conclude from our experiments that in vivo endothelial α-adrenergic receptors are solely responsible for the increased peripheral resistance; other agents such as angiotensin II and serotonin are likely to have similar dual effects on vascular reactivity. Therefore, ETA receptor blockade alone may have little effect, since these receptors are desensitized. On the other hand, ETB receptor inhibition may prevent hyperreactivity to agonists, which would act via the endothelium to release ET-1 and induce constriction. It remains to be proven that this mechanism is functional in humans and most importantly that the respective role of ETA and ETB receptors observed in rats is relevant to the human cardiovascular system.

In conclusion, our data support the concept that endogenous production of ET-1, derived from the endothelium, modulates the sensitivity of α-adrenergic and ET-1 contractile responses in rat cerebral vessels. This effect is mediated by smooth muscle ETB receptors, whereas ETA receptors are involved in the contractile response to ET. α2-Adrenergic responses are more complex and depend on both endothelial and smooth muscle responses. After 1 week of ET-1 treatment, smooth muscle cell sensitivity is decreased, whereas the overall vascular resistance increase is most likely due to an increased endothelial cell ET-1 release on hormonal stimulation. Compared with the mesenteric circulation, cerebral vessels would be more sensitive to α-adrenergic stimulation and possibly to hormones acting via a similar constricting pathway involving endothelium-derived ET-1 such as angiotensin II and serotonin.

Acknowledgments

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Vascular Effect of Hyperendothelinemia

It has been suggested that levels of circulating ET-1 reached in atherosclerotic patients may promote vascular spasm. Our results partly confirm this hypothesis, since ET-1 treatment favored constriction to α-adrenergic stimulation in cerebral vessels. This, however, appears to be an agonist-specific effect because both PE- and ET-1-mediated contractions were unaffected in treated rats. Furthermore, there was a clear decrease in smooth muscle cell sensitivity to agonists observed in denuded cerebral and MES arteries. Consequently, it is difficult to reconcile the decrease in smooth muscle sensitivity with the increase in systemic vascular resistance revealed by the increase in blood pressure. The effects of ET-1 treatment on α-adrenergic responses, however, reveal that the cardiovascular system has means to compensate for this loss in sensitivity. It is likely that responses of hormones whose actions are partly dependent on an endothelium-dependent response associated with the release of ET-1 are exacerbated in our experimental model.

The decrease in smooth muscle cell sensitivity to contractile agonists appears to be partly associated with a decrease in ETa receptor sensitivity and/or number. Both ET-1– and PE-induced contraction were unaffected by BQ123 in ET-1–treated rat cerebral arteries as opposed to the control response. It is most likely that the rise in [ETa] induced ETa receptor desensitization and/or downregulation. Although not comparable to this study, Chester and coworkers reported that ET-1 sensitivity was decreased in coronary vessels isolated from atherosclerotic patients, a condition associated with increased circulating ET-1 levels. ETb receptors, on the other hand, do not seem to be affected by the treatment, since the maximal response and the sensitivity to ET-1 were similar in the presence of BQ123 in treated and control rats. Once again, although our model is not related to atherosclerosis, it has been shown that the level of expression of ETb receptors increased in coronary arteries of atherosclerotic patients.

In the mesenteric bed, neither PE nor OXY induced contraction in the presence of an intact endothelium. It is known that in small rat MES arteries, sensitivity to PE is lower than in large MES vessels. Because OXY induced
References


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