Mechanisms of Endothelin-Induced Venoconstriction in Isolated Guinea Pig Mesentery

Ron J. Johnson, Gregory D. Fink, and James J. Galligan

ABSTRACT

In the present study, endothelin (ET) agonists and receptor selective antagonists were used to characterize ET receptors mediating constriction in guinea pig mesenteric veins (250–300 μm diameter) in vitro. The contribution of ET-evoked vasodilator release to venous tone was also explored. Computer-assisted video microscopy was used to monitor vein diameter. Endothelin-1 (ET-1), endothelin-3 (ET-3), and sarafotoxin 6c (S6c) produced sustained concentration-dependent contractions with a rank order agonist potency of ET-1 > S6c > ET-3. Indomethacin (1 μM) and Nω-nitro-arginine (100 μM) enhanced ET-1 and S6c responses. The ET_A selective antagonists BQ-610 (100 nM) and PD156707 (10 nM) shifted ET-1 concentration-response curves rightward and decreased maximal ET-1 responses, without changing S6c responses. The ET_B selective antagonist BQ-788 (100 nM) shifted S6c responses rightward but produced no change in ET-1 responses. Combined application of BQ-788 and BQ-610 or BQ-788 and PD 156707 produced a rightward shift in ET-1 responses that was greater than shifts produced by BQ-610 or PD 156707 alone. In conclusion, smooth muscle in guinea pig mesenteric veins expresses ET_A and ET_B receptors coupled to contractile mechanisms. Activation of endothelial ET_B receptors results in release of vasodilators, primarily nitric oxide.

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ABBREVIATIONS: BQ-610, (N,N-hexamethylenecarbamoyle-Leu-γ-Trp(CHO)-o-Trp; BQ-788, N-cis-2,6-dimethylpiperidinocarbonyl-γ-MeLeu-o-Trp (COOCH3)-Nle; EC50, half-maximal effective molar concentration; E_max, maximum contraction; ET, endothelin; NLA, Nω-nitro-arginine; NO, nitric oxide; NOS, nitric oxide synthase; PD 156707, [sodium 2-benzo[1.3]dioxol-5-yl-4-(4-methoxy-phenyl)-4-oxo-3-(3,4,5-trimethoxy-benzyl)-but-2-enolate]; PGI2, prostacyclin; S6c, sarafotoxin 6c; VSM, vascular smooth muscle.
ined the effects of ETs on veins. Studies in vitro consistently show that maximal responses and potency for ETs in veins are greater than those of corresponding arteries (Cocks et al., 1989; Riezebos et al., 1994; Rubanyi and Polakoff, 1994). Venous systems such as the mesenteric veins serve a large capacitance function. ET-induced alterations in their tone could result in significant changes in blood volume distribution, cardiac output, and blood pressure (Waite and Pang, 1990; Monos et al., 1995). Therefore, examination of ET receptors mediating venoconstriction in the mesentery will provide a better understanding of ET’s potential contribution to physiologic control of body fluid distribution and blood pressure. In the present study, ET agonists and receptor-specific antagonists were used to characterize ET receptor subtypes mediating venoconstriction in guinea pig mesenteric veins in vitro. Furthermore, the contribution of ET-evoked vasodilator release to venous tone was also explored.

Materials and Methods

Tissue Preparation. Male guinea pigs (Michigan Department of Public Health, Lansing, MI) 325 to 350 g were anesthetized lightly via halothane inhalation, stunned, and bled from the neck. The ileum and associated mesenteric vessels (including the root of the mesentery) were removed and placed in oxygenated (95% O2/5% CO2) Krebs’ solution of the following composition: 117 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl2, 1.2 mM MgCl2, 25 mM NaHCO3, 1.2 mM NaH2PO4, and 11 mM glucose. A segment of ileum (5 cm) with associated mesenteric vessels was removed and pinned flat in a silicone elastomer-lined Petri dish. A section of mesentery containing vessels close to the mesenteric border was cut out using fine scissors and forceps. The preparation was transferred to a smaller silicone elastomer-lined recording bath (5–6 ml volume) and pinned flat. Veins approximately 250 to 300 μm in diameter (mean diameter 281 ± 17 μm) were isolated by clearing surrounding arteries and other tissue. Isolated vessels were placed under no predetermined transmural pressure. The chamber was then mounted on the stage of an inverted microscope (Olympus CK-2; Lecor Corp., St. Joseph, MI) and superfused with warm (36°C) Krebs’ solution at a flow rate of 7 ml/min. All preparations were allowed a 15-min equilibration period during which time all vessels relaxed to a stable resting diameter.

Video Monitoring of Vessel Diameter. The methods used to monitor the diameter of mesenteric veins were identical with those described by others (Neild, 1989; Galligan et al., 1995). The output of a black and white video camera (Hitachi, KP-111; Lecor Corp.) attached to the microscope was fed to a PCVision Plus frame-grabber board (Image Technology Inc. Woodburn, MA) mounted in a personal computer. The video images were analyzed using Diamtrak computer software (Neild, 1989). The digitized signal was converted to an analog output (DAC-02 board, Keithley Megabyte, Taunton, MA) and fed to a chart recorder (Gould Inc., 2400s, Cleveland, OH) for an online record of vessel diameter. The sampling rate was 10 Hz, and changes in vessel diameter of 0.5 μm could be resolved.

Experimental Protocols. Preparations were superfused with Kreb’s solution and allowed a 15-min equilibration period before addition of drug. Agonist concentration-response curves were generated using cumulative application of increasing agonist concentrations. Previous studies revealed no difference in concentration-dependent contractile responses to ET applied cumulatively versus single-dose application. ET-1, ET-3, and S6c dissociate from receptor sites very slowly resulting in prolonged washout periods, therefore individual preparations were tested with one agonist only, with each concentration-response reaching a maximum (5–6 min) before addition of the next concentration of agonist (Waggoner et al., 1992). Contributions from dilators released by ET-1 and S6c were studied by pretreatment of preparations with the cyclooxygenase inhibitor, indomethacin (1 μM) and the nitric oxide synthase (NOS) inhibitor Nω-nitro-L-arginine (NLA; 100 μM). In a separate experiment the effects of indomethacin (1 or 10 μM) or NLA (100 μM) on ET-1 concentration responses were examined. Indomethacin and/or NLA were applied for 20 min before agonist application. The relative contributions of ETα and ETβ receptors to contractile responses was studied by comparing curves for ET-1 and S6c in the presence and absence of the ETα receptor-selective antagonists PD 156707 or BQ-610 and/or the ETβ receptor selective antagonist BQ-788. All ET antagonist experiments were conducted in the presence of indomethacin (1 μM) and NLA (100 μM) to study ET-1- and S6c-evoked constrictor responses in the absence of dilator release.

Analysis of Responses. For the comparison of agonist responses, a complete concentration-response curve for an agonist was obtained for a given preparation. Contractions were expressed as percentage of decrease in resting vessel diameter, where the resting vessel diameter after initial equilibration period was taken to be baseline. Concentration-response curves were fit by a 4-parameter logistic concentration-response equation given as Y = [(A1 − A2)/(1 + (X − X0)5)] + A2. The derived parameters EC50 (X0; concentration generating half-maximal response) and maximum response or Emax (A2) were expressed as the mean ± S.E.M. and n values refer to the number of preparations from which the data were obtained. Minimum response (A1; threshold response) and slope factor (P) were not significantly different across any experiment and therefore not reported. Statistical difference between means was determined by the Student’s two-tailed, unpaired t test. P < .05 was considered statistically significant. Analyses was conducted on a PC using ORIGIN software (Microcal software, Northampton, MA).

Drugs. ET-1, ET-3, S6c, BQ-788 (N-(ε-2,6-dimethylperidino-carbonyl-L-γ-MeLeu-ω-Trp (COOCH2-NH2)), and BQ-610 (N,N-hexamethylene/carbamoyl-Leu-ω-Trp(CH2-)NH2) were purchased from Peninsula Laboratories (Belmont, CA.). PD 156707 (sodium 2-benzol[1,3]dioxol-5-y1-4(4-methoxy-phenyl)-4-oxo-3(3,4,5-trime-thoxy-benzyl)-but-2-enato) was a generous gift from Parke-Davis Pharmaceuticals Research (Ann Arbor, MI). All other drugs were obtained from Sigma (St. Louis, MO). Stock solutions of NLA were prepared in 1 part hydrochloric acid (1 N) to 9 parts deionized water, whereas BQ-788 and BQ-610 were prepared in 1 part acetic acid (1 N) to 1 part deionized water. PD 156707 was prepared in deionized water. Indomethacin was prepared in dimethyl sulfoxide. Prazosin was prepared in 1 part methanol (100%) to 1 part deionized water. All other drugs were prepared as stock solutions in deionized water.

Results

Concentration Responses to ET-1, ET-3, and S6c. ET-1 (0.01–10 nM), ET-3 (0.01–10 nM), and S6c (0.01–10 nM) produced sustained concentration-dependent contractions (decreases in vessel diameter) in guinea pig mesenteric veins. To establish that contractions to ETs were through direct activation of ET receptors on VSM, preparations were pretreated for 20 min with either tetrodotoxin (300 nM), guanethidine (10 μM), or prazosin (1 μM) before application of agonists. Agonist responses in the presence of tetrodotoxin, guanethidine, or prazosin were unaffected when compared with control responses (data not shown). ET-1 concentration-response curves were left shifted compared with curves for ET-3, establishing a rank order potency of ET-1 > ET-3. The maximum contraction (Emax) caused by ET-1 was not different than ET-3. The Emax produced by ET-1 was greater than S6c, however, the two agonists were equipotent (Fig. 1 and Table 1).

Effects of Indomethacin and NLA on Dilator Contribution to Venous Tone. To evaluate the contributions of vasodilator substances to ET-1- and S6c-induced venous tone
in guinea pig mesentery, preparations were pretreated with indomethacin (1 \( \mu \)M) and NLA (100 \( \mu \)M) for 20 min before agonist addition. Indomethacin and NLA produced no change in resting vessel diameter. Contractions to ET-1 and S6c were enhanced in the presence of indomethacin and NLA when compared with control responses (Fig. 2 and Table 1). In a separate experiment the effects of indomethacin or NLA on ET-1 concentration responses were examined. Indomethacin at 1 or 10 \( \mu \)M produced no differences in ET-1 responses when compared with control values, however, NLA at 100 \( \mu \)M shifted ET-1 responses leftward and increased maximal responses when compared with control values (Fig. 3 and Table 1). All of the remaining experiments were done in the presence of indomethacin (1 \( \mu \)M) and NLA (100 \( \mu \)M).

**Effects of Antagonists on ET-1 and S6c Responses.** Cumulative concentration-response curves were obtained for ET-1 and S6c in the absence and presence of the ETA receptor-selective antagonists PD 156707 (1 \( \mu \)M, 100 nM, and 10 nM) and BQ-610 (100 nM), and the ET\(_B\) receptor-selective antagonist BQ-788 (100 nM). Pretreatment of preparations with antagonists for 20 min before agonist application produced no change in resting vessel diameter. S6c concentration-response curves in the presence of BQ-788 were shifted rightward when compared with control S6c responses, whereas BQ-610 did not change S6c responses (Fig. 4A and Table 2). PD 156707 at 1 \( \mu \)M or 100 nM produced rightward shifts in S6c concentration responses (data not shown), whereas PD 156707 at 10 nM did not change S6c responses when compared with control S6c values (Fig. 4B and Table 2). ET-1 concentration responses in the presence of BQ-610 showed a rightward shift and a decrease in the maximal response when compared with control ET-1 responses (Fig. 5A and Table 2). ET-1 responses in the presence of BQ-788 were not different when compared with control ET-1 responses (Fig. 5A and Table 2). PD 156707 (10 nM) decreased maximal ET-1 responses when compared with control ET-1 responses (Fig. 5B and Table 2). The combined application of BQ-788 and BQ-610 produced a rightward shift in ET-1 responses when compared with control ET-1 responses (Fig. 6B and Table 2) or to ET-1 responses in the presence of PD 156707 (10 nM) alone (Table 2).

**Discussion**

In the present study pharmacologic characterization of ET-receptor subtypes using ET-1-, ET-3-, S6c-, and ET-receptor selective antagonists revealed that guinea pig mesenteric

**Fig. 1.** Cumulative agonist concentration-response curves in guinea pig mesenteric veins. Agonist contractile-responses are expressed as a percentage of decrease of resting vessel diameter (resting vessel diameter represents baseline). Data are mean ± S.E.M. from \( n \) preparations.

**Fig. 2.** Indomethacin and NLA augment ET-1 and S6c concentration responses in guinea pig mesenteric veins. Indomethacin (1 \( \mu \)M) and NLA (100 \( \mu \)M) were applied for 20 min before application of S6c (A) or ET-1 (B). Agonist contractile responses are expressed as a percentage of decrease of resting vessel diameter (resting vessel diameter represents baseline). Data are mean ± S.E.M. from \( n \) preparations.

**Table 1**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( n )</th>
<th>( pD_2 )</th>
<th>( E_{\text{max}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1 (control)</td>
<td>6</td>
<td>9.17 ± 0.07</td>
<td>63.2 ± 8.1</td>
</tr>
<tr>
<td>ET-3 (control)</td>
<td>5</td>
<td>8.65 ± 0.11</td>
<td>41.3 ± 4.5</td>
</tr>
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<td>ET-1 + NLA 100 ( \mu )M</td>
<td>5</td>
<td>9.47 ± 0.23</td>
<td>82.2 ± 4.9</td>
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<td>Indo 1 ( \mu )M</td>
<td>5</td>
<td>8.89 ± 0.05</td>
<td>71.2 ± 5.2</td>
</tr>
<tr>
<td>ET-1 + Indo 1 ( \mu )M</td>
<td>4</td>
<td>8.83 ± 0.04</td>
<td>61.0 ± 9.0</td>
</tr>
<tr>
<td>ET-1 + Indo 10 ( \mu )M</td>
<td>5</td>
<td>8.94 ± 0.08</td>
<td>69.5 ± 4.0</td>
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<tr>
<td>ET-1 (control)</td>
<td>8</td>
<td>9.16 ± 0.07</td>
<td>57.6 ± 2.6</td>
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<tr>
<td>ET-1 + NLA 100 ( \mu )M</td>
<td>6</td>
<td>9.27 ± 0.03</td>
<td>78.1 ± 2.1</td>
</tr>
<tr>
<td>S6c (control)</td>
<td>6</td>
<td>9.17 ± 0.13</td>
<td>31.9 ± 5.8</td>
</tr>
<tr>
<td>S6c + NLA 100 ( \mu )M</td>
<td>6</td>
<td>9.67 ± 0.20</td>
<td>52.1 ± 2.9</td>
</tr>
<tr>
<td>Indo 1 ( \mu )M</td>
<td></td>
<td></td>
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</tbody>
</table>

Data are expressed as mean ± S.E.M.; \( n \) refers to number of preparations. Statistical comparisons were made by Student’s unpaired \( t \) test with a significance level of \( P < 0.05; \) \( pD_2 \) is negative logarithm of molar concentration of agonist producing half-maximal contraction (% decrease in diameter); \( E_{\text{max}} \) is maximum contraction based on data fitted to logistic equation. \( * \) Significant compared with control value; \( \# \) significant compared with corresponding ET-3 value; \( ^{\dagger} \) significant compared with corresponding S6c value.
veins possess $\text{ET}_A$ and $\text{ET}_B$ receptors coupled to contractile mechanisms. Our data also shows that activation of $\text{ET}_B$ receptors by ET-1 and S6c results in vasodilator release that reduces venoconstriction.

ET-1 and S6c induce the release of the NOS-derived vasodilator product NO and the cyclooxygenase-derived vasodilator product PGI2 by binding to $\text{ET}_B_1$ receptors on the endothelial cell membrane (Sakurai et al., 1992; Douglas et al., 1995). In the present study, pretreatment of preparations with indomethacin, which inhibits cyclooxygenase and NLA, an inhibitor of NOS, produced no changes to resting vessel diameter, suggesting that dilator release was evoked by ETs and not the result of basal release from the vessel. Our study did not examine the cell type expressing $\text{ET}_B_1$ receptors, but endothelial cells lining the venous lumen are the most likely source of the vasodilators (Sakurai et al., 1992; Douglas et al., 1995). PGI2 is the major product released by vascular cyclooxygenase, but its contribution to endothelium-dependent relaxation is minor (Shimokawa and Vanhoutte, 1997). However, others have shown that the cyclooxygenase inhibitor acetylsalicylic acid and not the NOS inhibitor $N^G$-monomethyl-$\text{l}$-arginine potentiated ET-1-induced venoconstriction in human dorsal hand veins in vivo (Webb and Haynes, 1993). Our findings in guinea pig mesenteric veins do not support a role for cyclooxygenase-derived dilators, but instead show that NO is the major dilator released in response to ET-1. Inhibition of NOS and cyclooxygenase removes ET-1- and S6c-evoked dilator contributions to net vessel tone, leaving ET-induced VSM constrictor responses unopposed.

Fig. 3. NLA but not indomethacin augments ET-1 concentration responses in guinea pig mesenteric veins. Indomethacin (1 $\mu$M or 10 $\mu$M) (A) or NLA (100 $\mu$M) (B) were applied for 20 min before application of ET-1. ET-1 contractile responses are expressed as a percentage of decrease of resting vessel diameter (resting vessel diameter represents baseline). Data are mean ± S.E.M. from n preparations.

Fig. 4. Effects of ET$_A$-selective antagonists BQ-610 and PD 156707 and ET$_B$-selective antagonist BQ-788 on S6c concentration responses in guinea pig mesenteric veins. BQ-610 (100 nM) or BQ-788 (100 nM) (A) or PD 156707 (10 nM) (B) were applied in the presence of indomethacin and NLA for 20 min before S6c application. S6c contractile responses are expressed as a percentage of decrease of resting vessel diameter (resting vessel diameter represents baseline). Data are mean ± S.E.M. from n preparations.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$n$</th>
<th>$p_{D_2}$</th>
<th>$E_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1 (control)</td>
<td>12</td>
<td>9.01 ± 0.08</td>
<td>64.4 ± 3.6</td>
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<tr>
<td>+ BQ-788 (100 nM)</td>
<td>4</td>
<td>9.12 ± 0.04</td>
<td>70.0 ± 3.3</td>
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<tr>
<td>+ BQ-610 (100 nM)</td>
<td>7</td>
<td>8.82 ± 0.14</td>
<td>53.2 ± 4.3</td>
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<tr>
<td>ET-1 (control)</td>
<td>5</td>
<td>9.06 ± 0.13</td>
<td>48.7 ± 5.0</td>
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<tr>
<td>+ BQ-788 (100 nM)</td>
<td>5</td>
<td>7.99 ± 0.15$^{a,b}$</td>
<td>50.3 ± 4.4</td>
</tr>
<tr>
<td>BQ-610 (100 nM)</td>
<td>6</td>
<td>9.07 ± 0.30</td>
<td>65.7 ± 3.1</td>
</tr>
<tr>
<td>ET-1 (control)</td>
<td>5</td>
<td>9.47 ± 0.47</td>
<td>65.6 ± 6.2</td>
</tr>
<tr>
<td>+ BQ-788 (100 nM)</td>
<td>5</td>
<td>8.20 ± 0.20$^{a,c}$</td>
<td>56.7 ± 4.8</td>
</tr>
<tr>
<td>PD156707 (10 nM)</td>
<td>6</td>
<td>9.36 ± 0.11</td>
<td>51.6 ± 2.7</td>
</tr>
<tr>
<td>S6c (control)</td>
<td>4</td>
<td>7.08 ± 0.12$^a$</td>
<td>35.1 ± 13.1</td>
</tr>
<tr>
<td>+ BQ-788 (100 nM)</td>
<td>4</td>
<td>9.59 ± 0.08</td>
<td>55.0 ± 4.7</td>
</tr>
<tr>
<td>+ BQ-610 (100 nM)</td>
<td>4</td>
<td>9.44 ± 0.35</td>
<td>51.0 ± 10.9</td>
</tr>
<tr>
<td>S6c (control)</td>
<td>4</td>
<td>9.14 ± 0.24</td>
<td>46.5 ± 8.8</td>
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</table>

Data are expressed as mean ± S.E.M.; $n$ refers to number of preparations. Statistical comparisons were made by Student's unpaired t test with a significance level of $P < .05$. $p_{D_2}$ is negative logarithm of molar concentration of agonist producing half-maximal contraction (% decrease in diameter); $E_{\text{max}}$ is maximum contraction based on data fitted to logistic equation. $^a$ Significant compared with control value; $^b$ significant compared with ET-1 + BQ-610; $^c$ significant compared with ET-1 + PD 156707. All preparations contained 1 $\mu$M indomethacin and 100 $\mu$M NLA.
The present study shows that dilator release provides a significant contribution to S6c-induced changes in venous tone in guinea pig mesenteric veins. Comparison of ET-1 $E_{\text{max}}$ values in the presence and absence of indomethacin and NLA with corresponding S6c values shows that ET-1 $E_{\text{max}}$ values are greater than S6c responses, however, both ET-1- and S6c-evoked dilator release account for approximately a 20% reduction in venous tone (Table 1). Thus, dilator release by both agonists are comparable. This finding is supported by an equal affinity for all ET isoforms at the ETB$_1$ receptor (Sakurai et al., 1990).

Pharmacological characterization of ET receptor subtypes mediating vasoconstriction in guinea pig mesentery was carried out using ET receptor-specific agonists and ET receptor-selective antagonists. Concentration-response curves for the mixed ET agonists ET-1 and ET-3 show a rank order agonist potency of ET-1 > ET-3, thereby establishing the presence of ET$_A$ receptors in guinea pig mesenteric veins. Sustained concentration-dependent contractions caused by S6c also establishes the presence of ET$_{B2}$ constrictor receptors in guinea pig mesenteric veins. Application of indomethacin and NLA in all experiments conducted with ET antagonists allowed for characterization of ET-induced vasoconstrictor mechanisms in the absence of ET-evoked dilator contributions. The ET$_A$ selective antagonist BQ-610 at 100 nM did not affect responses to S6c, suggesting that at this concentration BQ-610 did not block ET$_{B2}$ receptors. Likewise, the ET$_A$ selective antagonist PD 156707 at 10 nM also showed no affect on S6c responses, whereas higher concentrations of the antagonist shifted S6c responses rightward, suggesting that higher concentrations of PD 156707 (100 nM or 1 μM) were blocking ET$_{B2}$ receptors. Application of BQ-610 (100 nM) or PD 156707 (10 nM) inhibited ET-1 responses, providing further support for the presence of ET$_A$ receptors in guinea pig mesenteric veins. The ET$_B$-selective antagonist BQ-788 (100 nM) shifted S6c responses rightward but had no effect on ET-1 responses. These findings suggest that although ET$_{B2}$ constrictor receptors are present on the VSM, ET-1 may not activate them, or that an interaction occurs between the ET$_A$ and ET$_{B2}$ receptors resulting in masking of the ET$_{B2}$-mediated contractile effect. An interaction between ET$_A$ and ET$_{B2}$ receptors is supported in the present study by the finding that combined application of BQ-788 (100 nM) and BQ-610 (100 nM) (A) or BQ-788 (100 nM) and PD 156707 (10 nM) (B) produced a rightward shift in ET-1 responses that is greater than BQ-610 (100 nM) alone or PD 156707 (10 nM) alone, respectively. Findings in other in vitro studies have also suggested the existence of an interaction between the ET$_A$ and ET$_{B2}$ receptors including vascular (Fukuroda et al., 1994; Mickley et al., 1997) and nonvascular preparations (Fukuroda et al., 1996). It has been suggested that ET$_A$ receptors are the major subtype mediating vasoconstriction.
in the arterial or high-pressure side of the cardiovascular system, whereas ETB receptors exert a significant constrictor role in low-pressure systems such as the venous circulation (Moreland et al., 1994; Davenport et al., 1995). The results of the present study, while clearly demonstrating the presence of ETB receptors as well as ETA receptors, also shows that responses mediated by these receptors are only revealed after ETB receptor blockade, in addition to effective ETA receptor antagonism. The mechanism behind the proposed interaction between ETA and ETB receptors is not understood but may involve interactions at the receptor level or through second messengers (Fukuroda et al., 1996). Biochemical studies examining receptor and second-messenger interactions should provide valuable insight into the mechanism behind the proposed receptor “cross talk”.

In conclusion, guinea pig mesenteric veins express endothelial and VSM ETB receptors as well as VSM ETA receptors. Activation of either ETA or ETB receptors on the VSM results in venoconstriction, however, the endogenous ET peptide ET-1 does not appear to activate the ETB receptor due to a proposed receptor cross talk mechanism resulting in the masking of the ETB receptor-mediated responses by ETA receptor activation. Finally, ET-1 acting at ETB1 receptors results in dilator release, which is largely NO mediated and provides a minor effect on net venous tone.

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We thank Heidi Curtiss, Karen Jagschitz, and Mandy McCrumb for their excellent technical assistance.

References