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Facilitation and inhibition by endothelin-1 of adrenal catecholamine secretion in anesthetized dogs

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Abstract

We examined the participation of endothelin ET_A and ET_B receptors in modulation by endothelin-1 of adrenal catecholamine secretion during cholinergic activation in pentobarbital-anesthetized dogs. Drugs were infused intra-arterially into the adrenal gland. Splanchnic nerve stimulation (1 and 3 Hz) increased adrenal catecholamine output in a frequency-dependent manner. Endothelin-1 (0.2, 0.6, and 2 ng/kg/min) enhanced the catecholamine response induced by the 3-Hz nerve stimulation. Under pretreatment with an endothelin ET_A receptor antagonist (*R*)-2-[(*R*)-2-[(*S*)-2-[[1-(hexahydro-1*H*-azepinyl)]carbonyl]amino-4-methylpentanoyl]amino-3-(2-pyridyl) propionic acid (FR139317) (1 μg/kg/min), endothelin-1 suppressed the 1- and 3- Hz nerve stimulation-induced catecholamine response in a dose-dependent manner. No inhibitory or facilitatory effect of endothelin-1 was observed under simultaneous pretreatment with FR139317 and an endothelin ET_B receptor antagonist *N-cis* 2,6-dimethylpiperidinocarbonyl-L-γ-methylleucyl-D-1-methoxycarbonyltryptophanyl-D-norleucine (BQ-788) (1 μg/kg/min) or under pretreatment with BQ-788 alone. These results suggest that in the dog adrenal gland, endothelin-1 facilitates and inhibits adrenal catecholamine secretion during cholinergic activation by stimulating endothelin ET_A and ET_B receptors, respectively.

Keywords: Endothelin ET_A receptor; Endothelin ET_B receptor; Splanchnic nerve stimulation; FR139317; BQ-788

1. Introduction

Endothelin-1, a 21-amino acid peptide that is released from vascular endothelial cells, has been suggested to play an important role in the control of cardiovascular functions and participate in pathophysiology of cardiovascular disease (Rubanyi and Polokoff, 1994; Schiffrin, 1995). Endothelin receptors are classified into main subtypes of ET_A and ET_B (Rubanyi and Polokoff, 1994). It is well known that endothelin ET_A and ET_B receptors located on vascular smooth muscle cells mediate vasoconstriction, whereas endothelin ET_B receptors located on vascular endothelial cells mediate vasodilation through production of vasodilator substances such as prostacyclin and nitric oxide (NO). Adding to these opposite vascular actions, endothelin-1 is suggested to cause inhibition (Takagi et al., 1991), and both inhibition and facilitation (Mutafova-Yambolieva and Westfall, 1998) of peripheral adrenergic neurotransmission.

The adrenal medulla contains endothelin precursors (Davenport et al., 1996), endothelin converting enzymes (Emoto and Yanagisawa, 1995; Xu et al., 1994), endothelin family peptides (Davenport et al., 1996), and both endothelin ET_A and ET_B receptors (Belloni et al., 1997). Endothelin-1 is reported to evoke adrenal catecholamine secretion (Belloni et al., 1997; Boarder and Marriott, 1991; Yamaguchi, 1997) through stimulation of endothelin ET_A receptors (Belloni et al., 1997; Yamaguchi, 1997). In addition, endothelin-1 and acetylcholine cause a synergistic increase in catecholamine release from superfused adrenal chromaffin cells (Ohara-Imaizumi and Kumakura, 1991). A previous report from our laboratory demonstrated that endothelin-1 enhanced catecholamine secretion induced by splanchnic nerve stimulation in the dog adrenal gland in vivo (Takeuchi et al., 1992). Therefore endothelins may also participate in the control of adrenal catecholamine secretion.

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However, little is known about the role of endothelin ET_A and ET_B receptors in adrenal catecholamine secretion during cholinergic stimulation. In this study, we examined the effect of endothelin-1 on adrenal catecholamine secretion induced by splanchnic nerve stimulation in the absence and presence of (*R*)-2-[(*R*)-2-[(*S*)-2-[[1-(hexahydro-1*H*-azepinyl)]carbonyl]amino-4-methylpentanoyl]amino-3-(2-pyridyl) propionic acid (FR139317), a selective endothelin ET_A receptor antagonist (Sogabe et al., 1993), and *N-cis* 2,6-dimethylpiperidinocarbonyl-L-γ-methylleucyl-D-1-methoxycarbonyltryptophanyl-D-norleucine (BQ-788), a selective endothelin ET_B receptor antagonist (Ishikawa et al., 1994), in anesthetized dogs.

2. Materials and methods

2.1. Animal preparation

The experiments were performed in mongrel dogs of either sex weighing 6–20 kg. After initial anesthesia with sodium pentobarbital (30 mg/kg, i.v.), a constant level of anesthesia was maintained throughout the experiments by i.v. infusion of sodium pentobarbital (4–6 mg/kg/h) with an infusion pump (Model 201B, Atom, Tokyo, Japan). Artificial respiration was performed with a ventilator (Model SN-480-4, Shinano, Tokyo, Japan) with room air at 18 strokes/min (20 ml/kg tidal volume). The surgical procedure used in the present study was described previously (Kimura et al., 1988). The left adrenal gland was exposed by a retroperitoneal flank incision, and a polyethylene catheter was inserted into the left adrenolumbar vein for collection of venous effluent blood from the adrenal gland. A thread was placed around the junction of the adrenolumbar vein with the abdominal vena cava. Adrenal blood samples were obtained by pulling the thread, thus occluding the adrenolumbar vein and causing a retrograde flow of blood. Blood samples of 1 ml were collected in chilled test tubes containing 6 mg of ethylenediaminetetraacetic acid disodium. When not being sampled, adrenal venous blood was returned directly to the vena cava. Coagulation of blood was prevented by an initial i.v. injection of sodium heparin (250 U/kg). Systemic blood pressure and heart rate were measured with a polygraph (Model RPM-6008M, Nihon Kohden, Tokyo, Japan) from signal converted by a pressure transducer (MPU-0.5, Nihon Kohden) simultaneously, and recorded on a heat-writing recticorder (Model RJG-4128, Nihon Kohden).

2.2. Administration of drugs into the adrenal gland

The procedure for intra-arterial administration of drugs into the adrenal gland was reported previously (Kimura et al., 1992). The left phrenicoabdominal artery was dissected to expose its origin from the abdominal aorta. A 27-gauge needle connected to Y-shaped polyethylene catheter was inserted into the phrenicoabdominal artery at its origin for intra-arterial infusion of drugs.

2.3. Splanchnic nerve stimulation

After the diaphragm was incised, the left splanchnic nerves were dissected free from surrounding tissue and cut. A bipolar platinum electrode was placed in contact with the distal end of the splanchnic nerves. The splanchnic nerves were stimulated for 6 min with rectangular pulses of 1 ms and 10 V (supramaximal voltage) delivered by an electronic stimulator (SEN-2101, Nihon Kohden). Stimulus frequency was raised stepwise from 1 to 3 Hz at 3-min intervals during a 6-min stimulus period.

2.4. Experimental protocol

The dogs were divided into four groups. In Group 1 ($n = 7$), the effects of endothelin-1 on splanchnic nerve stimulation-induced increases in catecholamine output were examined. Splanchnic nerve stimulation (1 and 3 Hz) was repeated four times at 40-min intervals. The first set of splanchnic nerve stimulation during vehicle infusion into the adrenal gland was regarded as a control. Endothelin-1 infusion (0.2, 0.6, and 2 ng/kg/min) was started 25 min before the start of the second, third, and fourth sets of splanchnic nerve stimulation.

In Group 2 ($n = 8$), the effects of endothelin-1 (0.2, 0.6, and 2 ng/kg/min) during FR139317 (1 μg/kg/min) infusion on the splanchnic nerve stimulation-induced increases in catecholamine output were examined. The protocol was the same as used in Group 1 except that infusion of FR139317 was started 25 min before the first set of splanchnic nerve stimulation and continued throughout the experiments.

In Group 3 ($n = 8$), the effects of endothelin-1 (0.2, 0.6, and 2 ng/kg/min) during BQ-788 (1 μg/kg/min) and FR139317 (1 μg/kg/min) infusion on the splanchnic nerve stimulation-induced increases in catecholamine output were examined. The protocol was the same as used in Group 1, except that infusion of FR139317 and BQ-788 was started 25 min before the first set of splanchnic nerve stimulation and continued throughout the experiments.

In Group 4 ($n = 9$), the effects of endothelin-1 (0.2, 0.6, and 2 ng/kg/min) during BQ-788 (1 μg/kg/min) infusion on the splanchnic nerve stimulation-induced increases in catecholamine output were examined. The protocol was the same as used in Group 1, except that infusion of BQ-788 was started 25 min before the first set of splanchnic nerve stimulation and continued throughout the experiments.

2.5. Blood sampling and determination of adrenal catecholamine output

In all Groups, adrenal venous blood was sampled before and during splanchnic nerve stimulation. Sampling during

the basal state was performed 2 min before the start of splanchnic nerve stimulation. The time required to collect 1 ml of blood served to estimate adrenal venous flow rate. Adrenal blood samples were centrifuged to obtain plasma samples. Catecholamines were extracted from plasma by the alumina adsorption method, and plasma epinephrine and norepinephrine concentrations were determined by high-performance liquid chromatography with electrochemical detection (Model LC-304, Bioanalytical Systems, IN, USA), as described previously (Kimura et al., 1988). Adrenal epinephrine and norepinephrine output (ng/min) were calculated by multiplying plasma epinephrine and norepinephrine concentrations (ng/ml) by adrenal plasma flow rate (ml/min). Adrenal plasma flow rate was determined from the adrenal venous flow and the hematocrit of adrenal venous blood. The basal catecholamine output was determined from samples collected before splanchnic nerve stimulation. The splanchnic nerve stimulation-induced increases in catecholamine output were calculated by subtracting the basal catecholamine output from that obtained during splanchnic nerve stimulation. A previous study performed in our laboratory (Kimura et al., 1988) had confirmed that arterial plasma catecholamine concentrations, in either basal or stimulated state, were significantly smaller than adrenal venous plasma catecholamine concentrations and did not affect the evaluation of adrenal catecholamine secretion.

2.6. Analysis of data

All data are expressed as means ± S.E. Multifactor repeated-measures analysis of variance (ANOVA) was applied to evaluate overall statistical significance of the effects of splanchnic nerve stimulation and the drug in each experimental group. The significance of differences between the control values and those during infusion of endothelin-1 at each dose was evaluated by single factor repeated measures ANOVA and Dunnett's test. Differences at $P < 0.05$ were considered to be statistically significant.

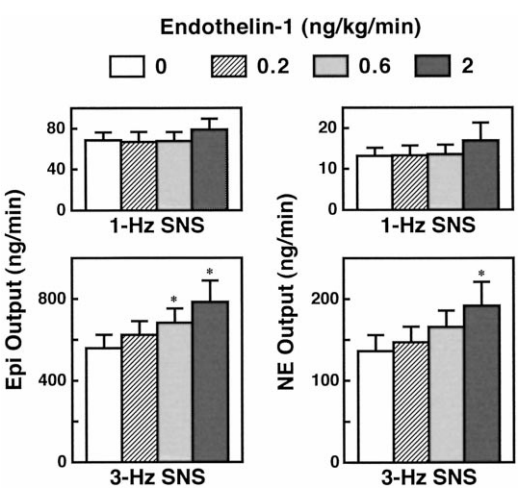

Fig. 1. Effects of endothelin-1 on epinephrine (Epi) and norepinephrine (NE) output from the adrenal gland in response to splanchnic nerve stimulation (SNS; Group 1, $n = 7$). Endothelin was infused into the adrenal gland via the phrenicoabdominal artery at the increasing doses. * $P < 0.05$ compared with the values before endothelin-1 infusion (zero dose).

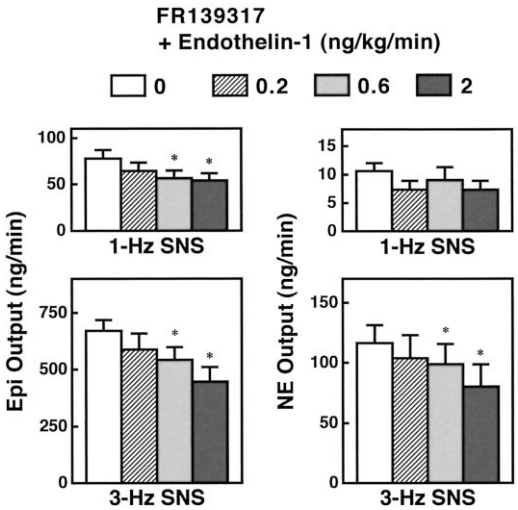

Fig. 2. Effects of endothelin-1 on epinephrine (Epi) and norepinephrine (NE) output from the adrenal gland in response to splanchnic nerve stimulation (SNS; Group 2, $n = 8$) in the presence of FR139317. FR139317 (1 μg/kg/min) was infused into the adrenal gland via the phrenicoabdominal artery throughout the experiments. Endothelin-1 was infused into the same artery at the increasing doses. * $P < 0.05$ compared with the values before endothelin-1 infusion (zero dose).

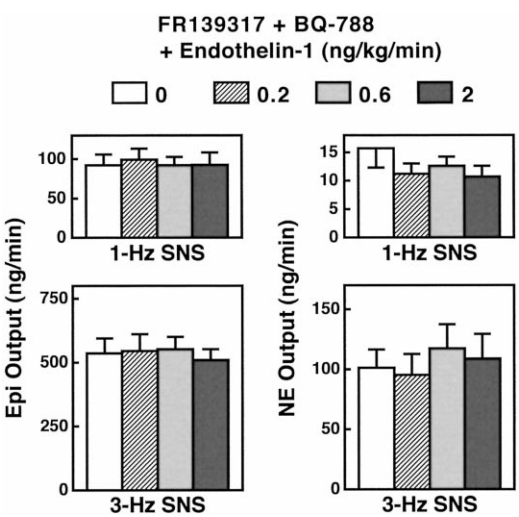

Fig. 3. Effects of endothelin-1 on epinephrine (Epi) and norepinephrine (NE) output from the adrenal gland in response to splanchnic nerve stimulation (SNS; Group 3, $n = 8$) in the presence of FR139317 and BQ-788. FR139317 (1 μg/kg/min) and BQ-788 (1 μg/kg/min) was simultaneously infused into the adrenal gland via the phrenicoabdominal artery throughout the experiments. Endothelin-1 was infused into the same artery at the increasing doses. There were no statistically significant differences between the corresponding values before endothelin-1 infusion (zero dose) and those obtained during endothelin-1 infusion.

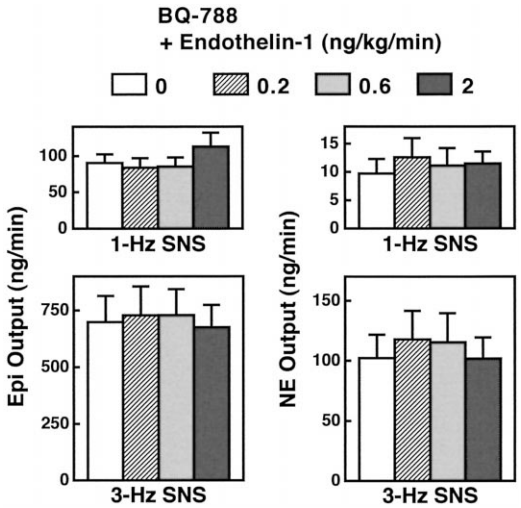

Fig. 4. Effects of endothelin-1 on epinephrine (Epi) and norepinephrine (NE) output from the adrenal gland in response to splanchnic nerve stimulation (SNS; Group 4, $n = 9$) in the presence of BQ-788. BQ-788 (1 μg/kg/min) was infused into the adrenal gland via the phrenicoabdominal artery throughout the experiments. Endothelin-1 was infused into the same artery at the increasing doses. There were no statistically significant differences between the corresponding values before endothelin-1 infusion (zero dose) and those obtained during endothelin-1 infusion.

2.7. Drugs

Endothelin-1 (Peptide Institute, Osaka, Japan) was dissolved in 0.1% acetic acid solution and diluted with 0.9% saline. BQ-788 (Banyu Pharmaceutical, Tsukuba, Japan) was dissolved in dimethylsulfoxide and diluted with 0.9% saline (the final concentration of dimethylsulfoxide in the drug solution was less than 1%). FR139317 (Fujisawa Pharmaceutical, Tsukuba, Japan) was dissolved in 0.9% saline.

3. Results

Splanchnic nerve stimulation (1 and 3 Hz) produced frequency-dependent increases in adrenal venous plasma epinephrine and norepinephrine concentrations (data are not shown) and catecholamine output (epinephrine and norepinephrine output; Figs. 1–4) calculated from the plasma concentrations and the adrenal plasma flow.

Infusion of endothelin-1 (0.2, 0.6, and 2 ng/kg/min) into the adrenal gland enhanced 3-Hz splanchnic nerve stimulation-induced increases in catecholamine output (Group 1; Fig. 1). The 1-Hz nerve stimulation-induced response remained unaffected. Endothelin-1 did not affect basal catecholamine output in any experimental groups (Table 1).

Under pretreatment with FR139317 (1 μg/kg/min; Group 2), endothelin-1 suppressed both the 1-Hz and 3-Hz nerve stimulation-induced increases in catecholamine output in a dose-dependent manner (Fig. 2). The suppression by endothelin-1 was not observed under combined pretreatment with FR139317 and BQ-788 (1μg/kg/min each; Group 3; Fig. 3). Under pretreatment with BQ-788 (1

Table 1
Effects of endothelin-1 (ET-1) in the presence or absence of endothelin antagonists on mean arterial pressure (MAP), heart rate (HR), epinephrine (Epi), and norepinephrine (NE) output and adrenal plasma flow rate (APF) under basal conditions
Values are means ± S.E. *n*, number of dogs.

	MAP (mm Hg)	HR (beats/min)	Epi output (ng/min)	NE output (ng/min)	APF (ml/min)
Non-pretreated (Group 1, n = 7)					
Control	117 ± 6	108 ± 11	3.1 ± 1.2	1.0 ± 0.4	1.1 ± 0.2
ET-1 0.2 ng/kg/min	113 ± 6	105 ± 11	2.2 ± 0.6	0.7 ± 0.2	1.0 ± 0.1
ET-1 0.6 ng/kg/min	111 ± 8[a]	104 ± 12[a]	2.4 ± 0.7	0.9 ± 0.3	0.9 ± 0.1[a]
ET-1 2 ng/kg/min	110 ± 9[a]	101 ± 12[a]	2.6 ± 0.9	0.5 ± 0.1	0.8 ± 0.1[a]
FR139317 1 μg / kg / min (Group 2, n = 8)					
FR139317	102 ± 6	99 ± 7	4.3 ± 1.0	0.9 ± 0.4	1.5 ± 0.2
+ ET-1 0.2 ng/kg/min	97 ± 5[a]	95 ± 7[a]	4.2 ± 1.1	1.2 ± 0.3	1.4 ± 0.2
+ ET-1 0.6 ng/kg/min	93 ± 5[a]	91 ± 6[a]	4.5 ± 1.3	1.0 ± 0.2	1.3 ± 0.2[a]
+ ET-1 2 ng/kg/min	88 ± 6[a]	89 ± 6[a]	3.6 ± 0.7	0.9 ± 0.2	1.1 ± 0.2[a]
FR139317 1 μg / kg / min + BQ-788 1 μg / kg / min (Group 3, n = 8)					
FR139317 + BQ-788	131 ± 6	150 ± 10	4.0 ± 1.2	1.4 ± 0.3	1.8 ± 0.2
+ ET-1 0.2 ng/kg/min	129 ± 6[a]	147 ± 10	3.6 ± 1.0	1.4 ± 0.5	1.9 ± 0.2
+ ET-1 0.6 ng/kg/min	129 ± 6[a]	144 ± 10[a]	5.1 ± 1.1	1.8 ± 0.6	1.8 ± 0.2
+ ET-1 2 ng/kg/min	126 ± 6[a]	140 ± 10[a]	6.0 ± 2.3	1.9 ± 0.5	1.8 ± 0.2
BQ-788 1 μg / kg / min (Group 4, n = 9)					
BQ-788	125 ± 5	138 ± 6	3.2 ± 0.7	2.1 ± 0.6	1.8 ± 0.2
+ ET-1 0.2 ng/kg/min	122 ± 5	133 ± 6[a]	4.1 ± 1.1	2.0 ± 0.5	1.6 ± 0.2[a]
+ ET-1 0.6 ng/kg/min	118 ± 5[a]	129 ± 5[a]	4.6 ± 1.4	1.3 ± 0.4	1.3 ± 0.2[a]
+ ET-1 2 ng/kg/min	116 ± 5[a]	125 ± 5[a]	3.9 ± 0.8	0.9 ± 0.1	1.1 ± 0.1[a]

[a] $P < 0.05$ compared with the values before endothelin-1 infusion.

μg/kg/min; Group 4), endothelin-1 failed to affect the nerve stimulation-induced increases in catecholamine output (Fig. 4).

Basal adrenal plasma flow rate decreased during endothelin-1 infusion alone (Group 1), which was also observed in the presence of FR139317 (Group 2) or BQ-788 (Group 4) but not in the presence of FR139317 and BQ-788 (Group 3; Table 1).

Mean arterial pressure before infusion of FR139317 (Group 2) was 105 ± 6 mm Hg, which was significantly lower ($P < 0.05$, one-way ANOVA and Dunnett's test) than the values before infusion of FR139317 and BQ-788 (Group 3; 132 ± 5 mm Hg) and infusion of BQ-788 (Group 4; 127 ± 5 mm Hg). Although these values were not different from the values before endothelin-1 infusion shown in Table 1 (Groups 2–4), slight reductions in arterial pressure and heart rate were observed during the experiments in all groups (Table 1).

4. Discussion

This study was performed to elucidate modulation by endothelin-1 of neural control of adrenal catecholamine secretion in relation to participation of endothelin ET_A and ET_B receptors. Effects of endothelin-1 on adrenal catecholamine (epinephrine and norepinephrine) secretion induced by splanchnic nerve stimulation were examined in the absence and presence of a selective antagonist for each endothelin receptor subtype and their combination in anesthetized dogs in vivo. We had previously confirmed that the catecholamine secretion response was reproducible when the nerve stimulation was applied four times without drug administration (Nagayama et al., 1998). Systemic blood pressure and heart rate slightly decreased during the experiments in the present study. However, these changes may not affect interpretation of results because the changes occurred in all experimental groups by the same extent.

Splanchnic nerve stimulation at 1 and 3 Hz increased adrenal catecholamine output in a frequency-dependent manner. Endothelin-1 infused intra-arterially into the adrenal gland enhanced the 3-Hz nerve stimulation-induced catecholamine response. These results are consistent with those obtained in our laboratory by intravenous injection of endothelin-1 (Takeuchi et al., 1992). Although we cannot explain why the 1-Hz nerve stimulation-induced response remained unaffected, this study demonstrates a facilitatory effect of endothelin-1 on the cholinergic adrenal catecholamine secretion. It has been reported that endothelin-1 induces catecholamine secretion from the dog adrenal gland (Yamaguchi, 1993, 1997) and bovine chromaffin cells (Boarder and Marriott, 1991) in the absence of cholinergic stimulation. However in this study, endothelin-1 did not affect basal adrenal catecholamine output. This difference may be due to the doses used at which plasma endothelin-1 concentration could not exceed the threshold to evoke catecholamine secretion in the dog adrenal gland. For example, in the dog adrenal gland, Yamaguchi (1993) observed catecholamine secretion during intra-arterial infusion of endothelin-1 at 50 and 500 ng/min for 1 min. In our study, endothelin-1 was infused at 0.2–2 ng/kg/min, which means that the doses were 4–40 ng/kg when administered to a dog of 20 kg body weight.

Under pretreatment with the endothelin ET_A receptor antagonist FR139317 (Sogabe et al., 1993), endothelin-1 suppressed the increases in catecholamine output induced by 1- and 3- Hz splanchnic nerve stimulation in a dose-dependent manner. The failure of endothelin-1 to enhance the catecholamine response indicates that its facilitatory effect observed in the non-pretreated dogs is mediated by endothelin ET_A receptors. Endothelin-1 is reported to evoke catecholamine secretion by stimulating endothelin ET_A receptors in the dog adrenal gland (Yamaguchi, 1997) and rat adrenomedullary cells (Belloni et al., 1997). However, there has been little information on the modulation by endothelin ET_A receptors of cholinergic control of adrenal catecholamine secretion. This study suggests that endothelin-1 enhances adrenal catecholamine secretion during cholinergic activation by stimulating endothelin ET_A receptors in dogs.

Stimulation of endothelin ET_B receptors inhibits adrenergic neurotransmitter release (Mutafova-Yambolieva and Westfall, 1998). Although endothelin ET_B receptors were suggested to play little role in the endothelin-1-evoked catecholamine secretion from the dog adrenal gland (Yamaguchi, 1997), we have recently found that the putative endothelin ET_B receptor agonist sarafotoxin S6c suppressed adrenal catecholamine secretion in response to cholinergic stimuli, and the suppression was prevented by pretreatment with the endothelin ET_B receptor antagonist BQ-788 in anesthetized dogs (Hosokawa et al., 1999). Endothelin ET_B receptors therefore seem to mediate the inhibitory effect of endothelin-1 on the splanchnic nerve stimulation-induced catecholamine response observed in the presence of FR139317. To confirm this possibility, we examined the effect of endothelin-1 under pretreatment with FR139317 and BQ-788. Combination of these antagonists abolished the inhibitory effect of endothelin-1 on the splanchnic nerve stimulation-induced catecholamine response, suggesting that endothelin-1 has an ability to inhibit adrenal catecholamine secretion during cholinergic activation through stimulation of endothelin ET_B receptors in dogs.

This study demonstrated the reciprocal effects of endothelin-1 through endothelin ET_A and ET_B receptors on adrenal catecholamine secretion. Therefore blockade of endothelin ET_B receptors would reveal the facilitatory role of endothelin ET_A receptors more clearly, but pretreatment with BQ-788 in the absence of FR139317 suppressed the facilitatory effect of endothelin-1 on the nerve stimulation-induced catecholamine response. This result raises questions about the roles of endothelin ET_A and ET_B receptors.

BQ-788 might also block endothelin ET_A receptors, but this is unlikely because BQ-788, as noted later, did not affect the endothelin-1-induced reduction in adrenal plasma flow. A possible explanation is that endothelin ET_B receptors could also play a stimulatory role in the adrenal catecholamine secretion when endothelin ET_A receptors are activated. We could postulate that stimulation of ET_B receptors amplifies the endothelin ET_A receptor-mediated signal transduction involved in the facilitation of catecholamine secretion. This modulation may be explained by assuming that the cross-talk between G protein-coupled receptors (Selbie and Hill, 1998), for example, stimulation of G_i-coupled endothelin ET_B receptors (Takagi et al., 1995) augments the G_q-coupled endothelin ET_A receptor-mediated phospholipase C activation. However, there is no direct evidence for this interaction in the dog adrenal gland. This issue requires further elucidation.

Endothelin-1 is known to induce vasoconstriction by stimulating endothelin ET_A and ET_B receptors and vasodilation by stimulating endothelin ET_B receptors (Rubanyi and Polokoff, 1994). It is suggested that stimulation of endothelin ET_A and ET_B receptors causes protein kinase C-dependent vasoconstriction and NO-dependent vasodilation, respectively, in the isolated perfused rat adrenal gland (Mazzocchi et al., 1998). However in this study, endothelin-1 reduced adrenal plasma flow rate, which was not suppressed by pretreatment with either FR139317 or BQ-788. Similar observations in the dog adrenal gland have been reported by Yamaguchi (1997). Other subtypes of endothelin receptors might mediate the endothelin-1-induced vasoconstriction, but combined pretreatment with FR139317 and BQ-788 abolished the endothelin-1-induced reduction in adrenal plasma flow rate. This result suggests that endothelin-1 induces vasoconstriction by stimulating either endothelin ET_A or ET_B receptors in the dog adrenal gland. Because no partial suppression with FR139317 or BQ-788 was observed, these vasoconstrictor mechanisms may compensate for each other.

In conclusion, this study demonstrated that in the dog adrenal gland in vivo (1) endothelin-1 enhanced adrenal catecholamine secretion in response to splanchnic nerve stimulation, (2) endothelin-1 suppressed the catecholamine secretion response under pretreatment with FR139317, and (3) the suppression by endothelin-1 in the presence of FR139317 was abolished by concomitant pretreatment with BQ-788. These results suggest that endothelin ET_A receptors play a facilitatory role, whereas endothelin ET_B receptors play an inhibitory role in cholinergic control of adrenal catecholamine secretion. Since BQ-788 failed to enhance the facilitatory effect of endothelin-1, there may be interactions between the endothelin ET_A and ET_B receptor-mediated mechanisms in the modulation by endothelin-1 of adrenal catecholamine secretion.

It should be noted, however, that the findings in the present study were obtained with exogenous endothelin-1. We failed to clarify physiological roles of endogenous endothelins in the adrenal gland; neither FR139317 nor BQ-788, when administered without endothelin-1, affected basal catecholamine output or the nerve stimulation-induced increases in catecholamine output (data are not shown). The present study revealed only pharmacological evidence for the modulation by endothelin receptors of adrenal catecholamine secretion.

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