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Role of endogenous endothelins in catecholamine secretion in the rat adrenal gland

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Abstract

We investigated the role of endogenous endothelins in catecholamine secretion in response to transmural electrical stimulation in the retrogradely perfused rat adrenal gland. (*R*)2-[(*R*)-2-[(*S*)-2-[[1-(hexahydro-1*H*-azepinyl)]carbonyl]amino-4-methyl-pentanoyl]amino-3-[3-(1-methyl-1*H*-indoyl)]propionyl]amino-3-(2-pyridyl) propionic acid (FR139317; 0.03–3 μM), an endothelin ET_A receptor antagonist, inhibited the electrical stimulation-induced epinephrine and norepinephrine output. Neither *N-cis*-2,6-dimethylpiperidinocarbonyl-L-γ-methylleucyl-D-1-methoxycarbonyltryptophanyl-D-norleucine (BQ-788; 0.03–3 μM), an endothelin ET_B receptor antagonist, nor phosphoramidon (1–100 mM), an endothelin-converting enzyme inhibitor, affected the catecholamine output responses. However, the inhibition by FR139317 of the catecholamine output responses was abolished by pretreatment with phosphoramidon (100 mM) or BQ-788 (3 μM). These results indicate that activation of endothelin ET_B receptors by endogenous endothelins inhibits the catecholamine output responses under the condition in which endothelin ET_A receptors are blocked. Exogenous endothelin-1 (1–100 nM) did not affect the catecholamine output responses, but it inhibited the responses under treatment with phosphoramidon and FR139317. Activation of endothelin ET_A receptors may interfere with the endothelin ET_B receptor-mediated inhibitory action on the neuronally evoked secretion of adrenal catecholamines.

Keywords: Endothelin-1; FR139317; BQ-788; Phosphoramidon; Transmural electrical stimulation

1. Introduction

Endothelin-1 is a 21-amino-acid vasoconstrictor peptide originally isolated from porcine endothelial cells in culture (Yanagisawa et al., 1988). There are at least three isopeptides of endothelin: endothelin-1, -2, and -3, which are generated from big endothelins by the endothelin-converting enzyme (Opgenorth et al., 1992; Turner and Murphy, 1996). Endothelins possess multiple specific binding sites of endothelin ET_A and ET_B receptors (Masaki et al., 1994; Rubanyi and Polokoff, 1994) that are widely distributed not only in the vascular system but also in the lungs, kidneys, brain and adrenal gland (Koseki et al., 1989).

Endothelin-1 directly stimulates the secretion of epinephrine and norepinephrine in cultured bovine adrenal chromaffin cells (Boarder and Marriott, 1989, 1991) and in the dog adrenal gland in vivo (Yamaguchi, 1993, 1995, 1997). Moreover, endothelin-1 enhances the secretion of adrenal catecholamines in response to acetylcholine in bovine adrenal chromaffin cells (Ohara-Imaizumi and Kumakura, 1991) and to splanchnic nerve stimulation in the dog adrenal gland (Hosokawa et al., 2000). These studies suggest that endothelin-1 is either directly or indirectly involved in local regulation of adrenal catecholamine secretion. Rat adrenomedullary chromaffin cells contain endothelin-converting enzyme (Takahashi et al., 1995), and bovine adrenomedullary chromaffin cells produce endothelin-1 (Sawamura et al., 1990). However, the contribution of endogenous endothelins to adrenal catecholamine secretion in the rat adrenal gland is not known.

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This study was undertaken to elucidate the functional role of endogenous endothelins in the secretion of adrenal epinephrine and norepinephrine. We examined the effects of endothelin-1, (*R*)2-[(*R*)-2-[(*S*)-2-[[1-(hexahydro-1*H*-azepinyl)]carbonyl]amino-4-methyl-pentanoyl]amino-3-[3-(1-methyl-1*H*-indoyl)]propionyl]amino-3-(2-pyridyl) propionic acid (FR139317), a selective endothelin ET_A receptor antagonist (Sogabe et al., 1993), *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), and phosphoramidon, an endothelin-converting enzyme inhibitor (Opgenorth et al., 1992), on the secretion of epinephrine and norepinephrine in response to transmural electrical stimulation in the isolated perfused rat adrenal gland.

2. Materials and methods

2.1. Animal preparation

All procedures for handling animals were approved by the Animal Experimentation Committee of Tohoku University Graduate School of Pharmaceutical Sciences. Male Wistar rats, weighing 250–350 g, were housed at 21–24°C and maintained on a standard diet and water ad libitum. Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). The surgical procedure was the same as previously described (Nagayama et al., 1999). A polyethylene cannula was inserted into the adrenal vein through the renal vein. Then the adrenal gland was carefully removed from the animal and a small slit was made into the adrenal cortex just opposite the entrance of the adrenal vein. Retrograde perfusion of the adrenal gland was started, to ensure that no leak was present, and the perfusate escaped only from the slit of the adrenal gland. The adrenal gland was placed on a bipolar platinum electrode used for transmural electrical stimulation. The adrenal gland together with the electrode was placed in a water-jacketed chamber maintaining the temperature of the adrenal gland at 37°C with thermostatically controlled water circulator (NTT-1200, EYELA, Tokyo, Japan). After removal of the adrenal gland, the animal was killed by exsanguination.

2.2. Perfusion of the adrenal gland

The adrenal gland was perfused by means of a peristaltic pump (MP-3A, EYELA) at a rate of 0.2 ml/min. The perfusion was carried out with Krebs–Henseleit solution of the following composition (mM): NaCl, 118; KCl, 4.7; $MgSO_4$, 1.2; $CaCl_2$, 2.6; KH_2PO_4, 1.2; $NaHCO_3$, 24.9; glucose, 11.1. Krebs solution was maintained at 37°C by the thermostat bath, and bubbled with a mixture of 95% O_2 and 5% CO_2. Perfusate samples were collected in chilled tubes containing 50 μl of 0.1 M perchloric acid, to prevent oxidation of catecholamines. Before starting a experiment, the adrenal gland was initially perfused for 60 min with Krebs solution.

2.3. Transmural electrical stimulation

Transmural electrical stimulation (duration, 1 ms; supramaximal voltage, 50 V) was applied by a bipolar platinum electrode with an electronic stimulator (SEN-3301, Nihon Kohden, Tokyo, Japan) and an isolation unit (SS-302J, Nihon Kohden). Stimulus frequency was raised stepwise from 1 to 2, 5 and 10 Hz at 5-min intervals, stimulation at each frequency being applied for 40 s.

2.4. Experimental protocol

The rats were divided into nine groups. In Group 1 ($n = 9$), the effects of repeated transmural electrical stimulation on catecholamine (epinephrine and norepinephrine) output were examined without drug treatment. A set of transmural electrical stimulation was repeated four times at 30-min intervals. In Group 2 ($n = 9$), the effects of endothelin-1 on catecholamine output induced by transmural electrical stimulation were examined. The first set of transmural electrical stimulation trials was regarded as a control. Perfusion with endothelin-1 (1, 10 and 100 nM)-containing Krebs–Henseleit solution was started 10 min before the second, third and fourth set of transmural electrical stimulations, respectively. In Groups 3 ($n = 8$), 4 ($n = 9$) and 5 ($n = 8$), the effects of FR139317 (0.03, 0.3 and 3 μM), BQ-788 (0.03, 0.3 and 3 μM) and phosphoramidon (1, 10 and 100 mM) on catecholamine output induced by transmural electrical stimulation were examined, respectively, with the same protocol as used in Group 2. In Group 6 ($n = 9$), the effects of FR139317 during treatment with BQ-788 on catecholamine output induced by transmural electrical stimulation were examined. Perfusion with BQ-788 (3 μM)-containing Krebs–Henseleit solution was started just after the completion of animal preparation. After the first set of transmural electrical stimulation trials, perfusion with FR139317 (0.03, 0.3 and 3 μM)- and BQ-788-containing Krebs–Henseleit solution was started 10 min before the second, third and fourth set of transmural electrical stimulations. In Group 7 ($n = 9$), the effects of FR139317 (0.03, 0.3 and 3 μM) during treatment with phosphoramidon (100 mM) on catecholamine output induced by transmural electrical stimulation were examined, with the same protocol as used in Group 6.

In Groups 8 ($n = 7$) and 9 ($n = 7$), the effects of endothelin-1 (100 nM) on the electrical stimulation-induced catecholamine output were examined in the presence of phosphoramidon (100 mM) and FR139317 (3 μM) or in the presence of phosphoramidon (100 mM),

FR139317 (3 μM) and BQ-788 (3 μM) with the same protocol as used in Group 6.

2.5. Perfusate sampling

Perfusate was sampled before and during transmural electrical stimulation to determine catecholamine output. The sampling during the basal state was performed for 60 s just before the electrical stimulation. In preliminary experiments, it was found that the electrical stimulation-induced catecholamine responses returned to pre-stimulation level within about 20 s after cessation of the stimulation. Thus, the sampling during the electrical stimulation at each frequency was performed for 60 s.

2.6. Determination of adrenal catecholamine output

Catecholamines in perfusate sample were measured by high-performance liquid chromatography with electrochemical detection (LC-4C, Bioanalytical Systems). Adrenal epinephrine and norepinephrine output (ng/min) were calculated by multiplying perfusate catecholamine concentration (ng/ml) by perfusion rate (0.2 ml/min). The basal catecholamine output was determined from sample collected just before each transmural electrical stimulation. The transmural electrical stimulation-induced catecholamine output were calculated by subtracting basal catecholamine output from that obtained during the stimulus state.

2.7. Analysis of data

The results are expressed as means ± S.E.M. Two-factor analysis of variance with Dunnett's test was used for statistical analysis of data. P values less than 0.05 were considered to be statistically significant.

2.8. Drugs

Endothelin-1 and phosphoramidon were purchased from Peptide Institute (Osaka, Japan). FR139317 and BQ-788 were kind gifts from Fujisawa Pharmaceutical (Osaka, Japan) and Banyu Pharmaceutical (Tsukuba, Japan), respectively. BQ-788 was dissolved in dimethyl sulfoxide and diluted to the required concentrations with Krebs–Henseleit solution. Other drugs were dissolved in Krebs–Henseleit solution.

3. Results

3.1. Catecholamine output in response to transmural electrical stimulation

Basal epinephrine and norepinephrine output from the adrenal gland at 60 min after initial perfusion with or without drugs were 20.8 ± 1.5 ng/min ($n = 77$) and 4.0 ± 0.3 ng/min ($n = 77$), respectively, in all groups. There were no differences in these basal values among the experimental groups. Transmural electrical stimulation (1, 2, 5 and 10 Hz) produced frequency-dependent epinephrine and norepinephrine output, and the output responses did not vary during the time course of the experiment (the four stimulation periods; Group 1, data not shown). The values were almost the same as those we had previously reported (Nagayama et al., 1999).

3.2. Effects of endothelin-1, FR139317, BQ-788 and phosphoramidon on the transmural electrical stimulation-induced catecholamine output

Endothelin-1 (1, 10 and 100 nM) did not affect the transmural electrical stimulation-induced epinephrine and norepinephrine output (Group 2). For example, the 10-Hz transmural electrical stimulation-induced epinephrine and norepinephrine output were 197 ± 35 ng/min ($n = 9$) and 50 ± 10 ng/min ($n = 9$) during control period, respectively, and 184 ± 42 and 49 ± 13 ng/min during treatment with 100-nM endothelin-1, respectively. FR139317 (0.03, 0.3 and 3 μM) significantly inhibited the transmural electrical stimulation-induced epinephrine and norepinephrine output (Group 3, Fig. 1A). Neither BQ-788 (0.03, 0.3 and 3 μM; Group 4) nor phosphoramidon (1, 10 and 100 mM; Group 5) affected the transmural electrical stimulation-induced epinephrine and norepinephrine output. The 10-Hz transmural electrical stimulation-induced epinephrine and norepinephrine output in Group 4 were 191 ± 23 ng/min ($n = 9$) and 52 ± 7 ng/min ($n = 9$) during control period, respectively, and 170 ± 26 and 42 ± 5 ng/min during treatment with 3-μM BQ-788, respectively, and the values in Group 5 were 198 ± 32 ng/min ($n = 8$) and 52 ± 4 ng/min ($n = 8$) during control period, respectively, and 168 ± 19 and 47 ± 4 ng/min during treatment with 100-mM phosphoramidon, respectively. Basal epinephrine and norepinephrine outputs were not affected by endothelin-1, FR139317, BQ-788 or phosphoramidon (data not shown).

3.3. Effects of FR139317 during treatment with BQ-788 or phosphoramidon

During treatment with BQ-788 (3 μM; Group 6, Fig. 1B) or phosphoramidon (100 mM; Group 7, Fig. 1C), the first transmural electrical stimulation-induced epinephrine and norepinephrine output were to the same degree as the values obtained in the control period of Group 3 (Fig. 1A). FR139317 (0.03, 0.3 and 3 μM) did not affect the transmural electrical stimulation-induced epinephrine and norepinephrine output under either condition. Basal epinephrine and norepinephrine outputs were not affected by FR139317 during treatment with BQ-788 or phosphoramidon (data not shown).

3.4. Effects of endothelin-1 during treatment with phosphoramidon and FR139317 or during treatment with phosphoramidon, FR139317 and BQ-788

Endothelin-1 (100 nM) significantly inhibited the transmural electrical stimulation-induced epinephrine output during treatment with phosphoramidon (100 mM) and FR139317 (3 μM) (Group 8, Fig. 2A). The norepinephrine output was also inhibited although the effect was not statistically significant. The inhibition was not observed during treatment with phosphoramidon (100 mM), FR139317 (3 μM) and BQ-788 (3 μM) (Group 9, Fig. 2B).

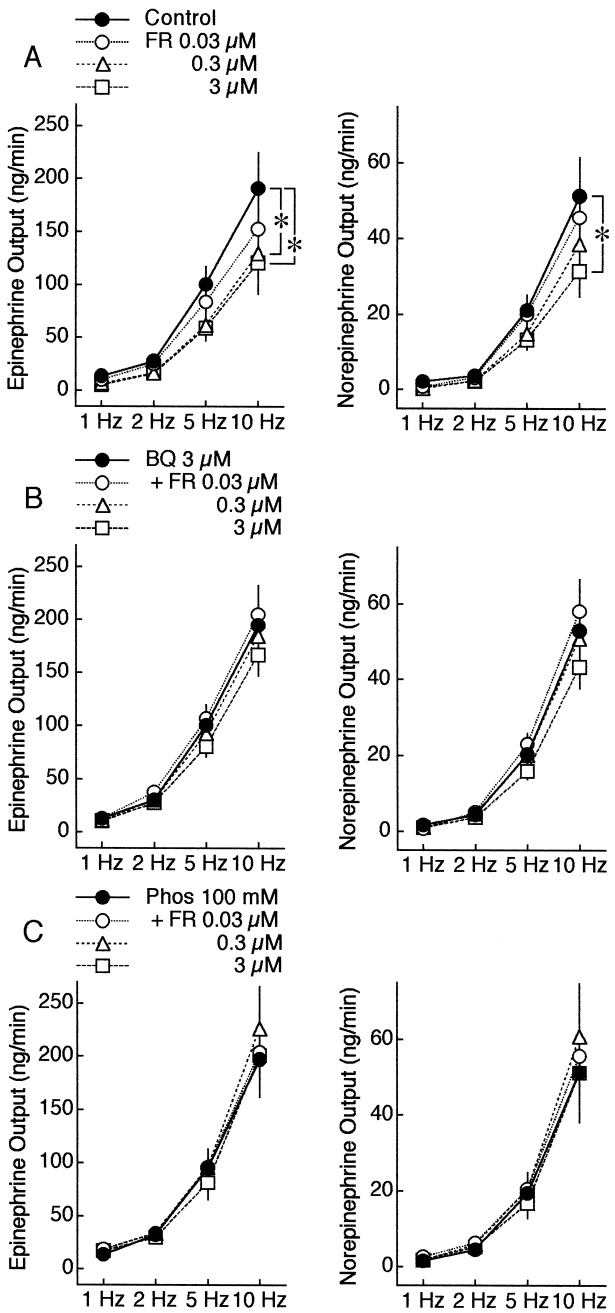

Fig. 1. Effects of FR139317 on the transmural electrical stimulation-induced epinephrine and norepinephrine output from the perfused adrenal glands in the absence (A; Group 3, $n = 8$) and presence of BQ-788 (B; Group 6, $n = 9$) or phosphoramidon (C; Group 7, $n = 9$). Symbols and vertical bars represent means ± S.E.M. $^{*}P < 0.05$ compared with corresponding control response obtained before the FR139317 treatment.

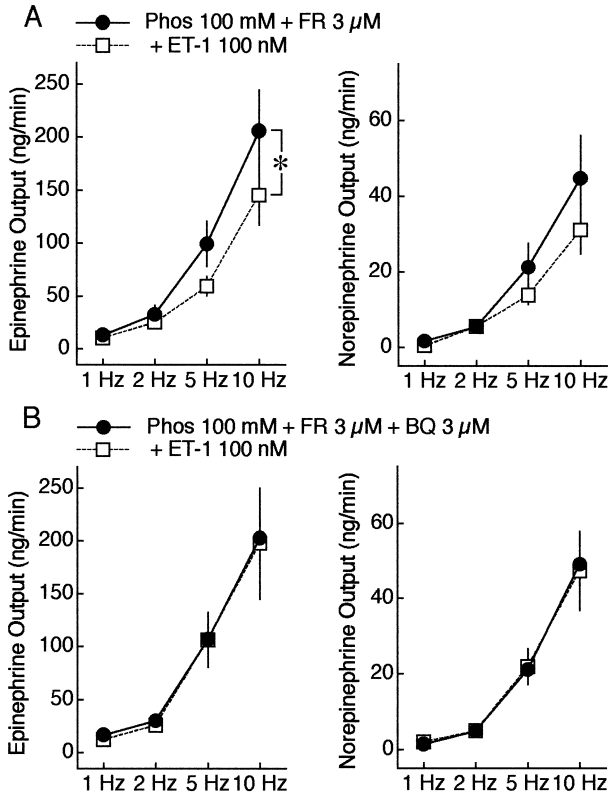

Fig. 2. Effects of endothelin-1 on the transmural electrical stimulation-induced epinephrine and norepinephrine output from the perfused adrenal glands in the presence of phosphoramidon and FR139317 (A; Group 8, $n = 7$) and of phosphoramidon, FR139317 and BQ-788 (B; Group 9, $n = 7$). Symbols and vertical bars represent means ± S.E.M. $^{*}P < 0.05$ compared with corresponding control response obtained before the endothelin-1 treatment.

4. Discussion

Transmural electrical stimulation caused marked epinephrine and norepinephrine output in a frequency dependent manner. We have previously observed that hexamethonium largely and atropine slightly inhibited the transmural electrical stimulation-induced secretion of epinephrine and norepinephrine under the same experimental conditions as in this study (Nagayama et al., 1999). Trasmural electrical stimulation may therefore cause release of acetylcholine from nerve terminals to induce catecholamine secretion by mainly activating nicotinic receptors on the surface of chromaffin cells. The catecholamine output responses were reproducible when the stimulation was applied in four consecutive experimental periods in the absence of drugs. Thus, the rat adrenal grand

preparation used in our experiments made it possible to examine the action of drugs on adrenal catecholamine secretion in response to endogenous acetylcholine.

However, it has been suggested that non-cholinergic transmitters also participate in the neural control of catecholamine secretion in the rat adrenal gland. Blockade of nicotinic and muscarinic receptors does not completely inhibit catecholamine secretion induced by transmural electrical stimulation at low frequencies for more than 5 min (Malhotra and Wakade, 1987), and the resistant portion of the catecholamine secretion can be related to peptides such as vasoactive intestinal polypeptide released from nerve terminals (Wakade et al., 1991; Guo and Wakade, 1994). The predominance of the cholinergic mechanism in our experiments may be due to conditions of the electrical stimulation. In our experiments the stimulation was applied for 40 s, which may not be sufficient to activate the non-cholinergic mechanism.

Endothelin-1 facilitates acetylcholine-evoked secretion of catecholamines in bovine adrenal cromaffin cells (Ohara-Imaizumi and Kumakura, 1991). A recent report from our laboratory suggested that endothelin-1 facilitates the splanchnic nerve stimulation-induced catecholamine secretion via activation of endothelin ET_A receptors in the dog adrenal gland in vivo (Hosokawa et al., 2000). In the present study, however, endothelin-1 did not affect the transmural electrical stimulation-induced epinephrine and norepinephrine output. Endothelin-1 might not modulate the neuronally evoked catecholamine secretion in the rat adrenal gland. However, the possibility remains that endogenous endothelins maximally affect the catecholamine secretion and thereby mask the effect of exogenous endothelin-1.

Adrenomedullary chromaffin cells have been reported to contain endothelin-converting enzyme (Sawamura et al., 1990; Takahashi et al., 1995) and produce endothelin-1 (Sawamura et al., 1990). These reports suggest that endogenous endothelins may play a modulatory role in the regulation of catecholamine secretion. To clarify this, we examined the effects of FR139317, a selective endothelin ET_A receptor antagonist, BQ-788, a selective endothelin ET_B receptor antagonist and phosphoramidon, an endothelin-converting enzyme inhibitor, on the transmural electrical stimulation-induced catecholamine output.

FR139317 significantly inhibited the transmural electrical stimulation-induced epinephrine and norepinephrine output. On the other hand, BQ-788 did not affect epinephrine and norepinephrine output induced by transmural electrical stimulation. These results might show that activation of endothelin ET_A receptors by endogenous endothelins facilitates the secretion of adrenal catecholamines, and that endothelin ET_B receptors have no role in the secretion. However, these seem unlikely, because phosphoramidon did not affect the transmural electrical stimulation-induced epinephrine and norepinephrine output, and because the inhibitory effect of FR139317 was blocked by either BQ-788 or phosphoramidon. These results suggest that endothelin ET_B receptors are involved in the FR139317-induced inhibition of the transmural electrical stimulation-induced catecholamine secretion. Activation of endothelin ET_B receptors by endogenous endothelins may inhibit the neuronally evoked catecholamine secretion under the condition in which endothelin ET_A receptors are blocked. The inhibitory action of endothelin ET_B receptors may be prevented by an endothelin ET_A receptor-mediated mechanism.

We also examined effects of exogenous endothelin-1 under treatment with phosphoramidon and FR139317. In this condition, endothelin-1 inhibited the transmural electrical stimulation-induced epinephrine and norepinephrine output, and the inhibition was blocked by BQ-877. These results could support the above-mentioned hypothesis for the role of endothelin ET_B receptors in the neuronally evoked adrenal catecholamine secretion.

Endothelin-1 (1–100 nM) did not affect basal epinephrine and norepinephrine output from perfused rat adrenal glands. It has been reported that 10-nM endothelin-1 directly stimulates the secretion of epinephrine and norepinephrine in cultured bovine adrenal chromaffin cells (Boarder and Marriott, 1989, 1991). Therefore, concentrations (1–100 nM) of endothelin-1 used in this study seem to be sufficient to stimulate catecholamine secretion. The lack of stimulatory effect of endothelin-1 on catecholamine secretion may be due to differences in the species examined or in experimental conditions.

In summary, this study demonstrated that the FR139317, but not BQ-788 or phosphoramidon, inhibited the transmural electrical stimulation-induced catecholamine output from the isolated rat adrenal gland. The inhibitory effect of FR139317 was abolished by phosphoramidon or BQ-788. Whereas exogenous endothelin-1 did not affect the transmural electrical stimulation-induced catecholamine output, treatment with FR139317 and phophoramidon revealed the ability of exogenous endothelin-1 to inhibit the catecholamine output that was susceptible to BQ-788. These results suggest that activation of endothelin ET_B receptors by endogenous endothelins inhibits the neuronally evoked secretion of catecholamines from the rat adrenal gland under the condition in which endothelin ET_A receptors are blocked. Activation of endothelin ET_A receptors may inhibit the endothelin ET_B receptor-mediated inhibitory action on the secretion.

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