Pharmacology Biochemistry and Behavior, Vol. 64, No. 1, pp. 171–176, 1999

0091-3057/99/$–see front matter

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PII S0091-3057(99)00123-9

Role of Endothelin Receptor Subtypes in the Behavioral Effects of the Intracerebroventricular Administration of Endothelin-1 in Conscious Rats

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Received 2 October 1998; Revised 9 March 1999; Accepted 25 March 1999

NAGASAKA, J., M. TSUJI, H. TAKEDA AND T. MATSUMIYA. *Role of endothelin receptor subtypes in the behavioral effects of the intracerebroventricular administration of endothelin-1 in conscious rats*. PHARMACOL BIOCHEM BEHAV **64**(1) 171–176, 1999.—The role of endothelin receptor subtypes, i.e., ET_A and ET_B receptors, in the behavioral effects of the intracerebroventricular (ICV) administration of endothelin-1 were examined in conscious rats. ICV administration of endothelin-1 (1–9 pmol/rat) dose dependently produced barrel rolling and other convulsive behaviors including bodily twitching, rigidity, back crawling, fore/hindlimb dystonia, fore/hindlimb clonus, tail extension, and facial clonus. Moreover, a marked increase in spontaneous locomotor activity was observed in animals that were treated with a low dose of endothelin-1 (1 pmol/rat, ICV). Endothelin-1 (9 pmol/rat, ICV)-induced barrel rolling and other convulsive behaviors were completely suppressed by the coadministration of BQ-123 (15 nmol, ICV), a specific endothelin ET_A receptor antagonist, but not of BQ-788 (15 nmol/rat, ICV), a specific endothelin ET_B receptor antagonist. In contrast, increased locomotor activity produced by treatment with a low dose of endothelin-1 (1 pmol/rat, ICV) was antagonized by coadministration of BQ-788, but not of BQ-123. These results indicate that endothelin-1, which has affinity for both endothelin ET_A and ET_B receptors, most likely acts on central ET_A receptors to evoke barrel rolling and other convulsive behaviors. In addition, activation of central ET_B receptors may be involved in the increase in spontaneous locomotor activity. These results suggest that brain endothelin receptor subtypes may be involved in the regulation of various physiological functions. © 1999 Elsevier Science Inc.

Endothelin-1 Behavior ICV BQ-123 BQ-788

ENDOTHELIN is a potent vasoconstrictive 21-amino acid peptide that was first isolated from the supernatant of endothelial cells by Yanagisawa et al. (40). Since then, the existence of three isoforms of endothelin has been demonstrated; i.e., endothelin-1, endothelin-2, and endothelin-3 (16,40). These isoforms have been identified in animals and humans. In addition, two binding sites for these peptides have been found; i.e., endothelin ET_A and ET_B receptor subtypes (1,37). The various physiological actions of the endothelins are mediated via interaction with these endothelin receptor subtypes (12,32).

Endothelin is widely distributed within the central nervous system (CNS). Indeed, endothelin-like immunoreactivity (6,13, 33), endothelin-converting enzyme activity (5,38), endothelin mRNA (7,28,30), and endothelin receptors (10,19,25,26) have been found in various regions of rat and human brain. The global distribution of endothelin and its binding sites in the brain suggest that it may be an important neuropeptide in the CNS (8). In particular, it has been proposed to act as a neurotransmitter or neuromodulator in the brain as well as a vascular autacoid that has numerous roles in normal and pathologic functions of several organs (18,29,34,41).

Recent behavioral pharmacological investigations have shown evidence that endothelin has stimulatory effects on cerebral function when injected in picomolar doses into a lateral ventricle of conscious rats. Intracerebroventricular (ICV) ad-

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ministration of endothelin-1 produces a characteristic behavior called barrel rolling, which is characterized by longitudinal rolling of the body, and/or provokes other abnormal convulsive behaviors (2,3,8,9,35). However, the roles of endothelin receptor subtypes, i.e., ET_A and ET_B receptors, in the expression of these convulsive behaviors produced by endothelin-1 are not yet clear. Therefore, we tried to confirm the mechanisms mediated by these two receptor subtypes in the abovementioned physiological manifestations of the central administration of endothelin-1 in conscious rats. To investigate the endothelin receptor subtype involved, we used the selective ET_A receptor antagonist BQ-123 (15) and the selective ET_B receptor antagonist BQ-788 (17).

METHOD

Animals and Surgery

Male Sprague–Dawley (SD) rats (Saitama Experimental Animals Supply Co., Ltd., Japan) weighing 220–300 g were housed at a room temperature of 23 ± 1°C with a 12-h light-dark cycle (light on 0600–1800 h). Food and water were available ad lib.

Rats were anesthetized with sodium pentobarbital (40 mg/kg, IP) and placed in a stereotaxic apparatus with the incisor bar 3.3 mm below the interaural line. Using bregma as a reference, we trephined a hole in the left parietal bone to expose the dural surface at coordinate +1.5 mm L and −0.8 mm P (36). A 20-gauge stainless steel guide cannulae was lowered 3.3 mm ventral from the dural surface into the lateral cerebral ventricle, and was secured to the skull with a cranial screw and dental cement. Removable obturators were inserted the full length of the cannulae to prevent obstruction by foreign substances and to limit infection. The rats were then returned to their individual home cages with food and water ad lib and allowed at least 48 h for recovery before use in the following experiments.

Drug Treatment

Endothelin-1 or vehicle was delivered into a lateral ventricle using a Hamilton syringe in a volume of 1.5 μl over a period of 30 s in accordance with the procedures by Chew et al. (3). In a combination study, BQ-123 or BQ-788 was coadministered with endothelin-1, also in a total volume of 1.5 μl. Each rat was used in only one experiment and received only one dose of the drugs. A small amount of Evans blue dye solution was injected into a lateral ventricle to confirm the accuracy of the drug administration at the end of the experiments.

Behavioral Measurement

Behavioral measurements on an open field (50 cm high, 60 cm in diameter) were recorded every 5 min until 60 min after the administration of vehicle or drugs. Behavioral assessments were based on a checklist of 13 parameters that were previously reported by Chew et al. (3) with a minor modification, including latency, duration numbers, and incidence of barrel rolling, locomotor activity, and the degrees of such observer-graded responses as bodily twitching, rigidity, back crawling, fore/hindlimb dystonia, fore/hindlimb clonus, tail extension, and facial clonus on a scale of 0 (absent), 1 (mild), 2 (moderate), and 3 (severe). Locomotor activity was measured by counting the number of line crossings in an open-field apparatus.

Drugs

The drugs used in the present study were endothelin-1 (Sigma Chemical Co., St. Louis, MO), BQ-123 (Banyu Pharmaceutical Co., Ltd., Japan) and BQ-788 (Banyu Pharmaceutical Co., Ltd. Japan). BA-788 was dissolved in 10% HCO-60 (Nikko Chemicals, Japan) solution in saline under stirring in a warm bath and adjusted to pH 7.0–7.5. All other drugs were dissolved in saline. The doses of BQ-123 and BQ-788 were determined refer to the previous reports using these antagonists (4,11,27,39). In our preliminary experiments, none of the rats receiving each antagonists exhibited a significant changes in locomotor activity compared with saline-treated rats [the means of locomotor activity (counts/1 h) were 214.9 ± 74.1, 206.1 ± 69.4, and 252.4 ± 56.5 in saline, BQ-123, and BQ-788 groups, respectively]. Also, other remarkable behavior changes were not observed by treatment with antagonists alone.

Statistical Analysis

The incidence of barrel-rolling behavior was statistically evaluated using means of 2 × 2 contingency tables and with Fisher's probability test. Other behavioral data were tested for significance with the nonparametric Kruskal–Wallis test because Bartlett's test for homogeneity of variances suggested that variances of data in some groups are not equal.

RESULTS

Behavioral Effects of ICV Administration of Endothelin-1

Behavioral changes produced by ICV administration of endothelin-1 are shown in Figs. 1 and 2 and Table 1. ICV administration of endothelin-1 (1–9 pmol/rat) to conscious rats produced a barrel-rolling behavior that was characterized by longitudinal rolling of the body. The incidence of animals that showed barrel rolling and the numbers and duration of this behavior increased in a dose-dependent manner, whereas the

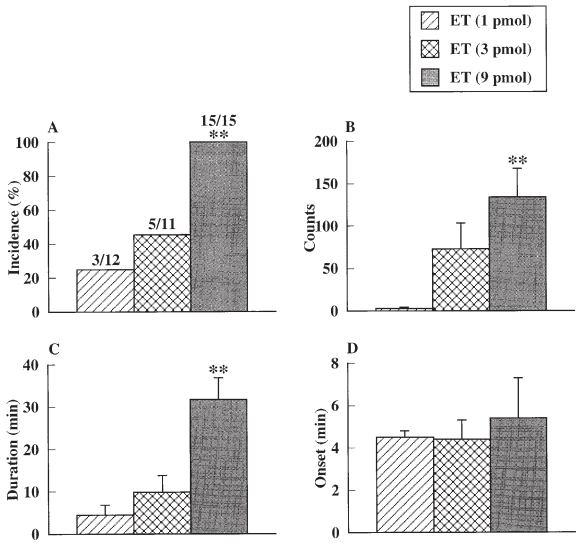

FIG. 1. Barrel-rolling behavior (A) Incidence; (B) counts; (C) duration; (D) onset produced by endothelin-1 (ET; 1–9 pmol/rat, ICV). Incidence of barrel-rolling behavior (A) was calculated as (positive/total rats) ×100. Each column in D represents the mean ± SEM of positive rats. $^{**}p < 0.01$ vs. saline-treated group.

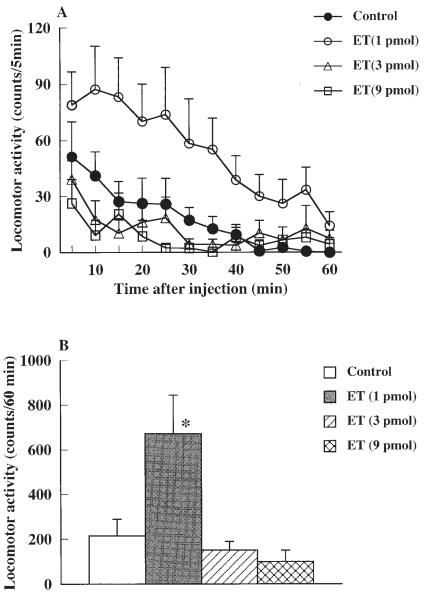

FIG. 2. Time course (A) and total counts (B) of changes in spontaneous locomotor activity produced by endothelin-1 (ET; 1–9 pmol/rat, ICV) in rats. Each point and column represents the mean ± SEM of 9–16 rats. *$p < 0.05$ vs. control group.

latencies to onset tended to remain constant independent of the dose administered, as shown in Fig. 1. Other types of convulsive activities, such as bodiy twitching, rigidity, back crawling, fore/hindlimb dystonia, fore/hindlimb clonus, tail extension, and facial clonus, were also produced by endothelin-1 (Table 1). Moreover, in the group that was treated with a low dose of endothelin-1 (1 pmol/rat, ICV), a specific increase in locomotor activity was observed (Fig. 2). However, this behavior was not observed any longer at higher doses of endothelin-1 (3 and 9 pmol/rat, ICV) because of the appearance of barrel-rolling and other convulsive behaviors.

Effects of Endothelin Receptor Subtype Antagonists on Endothelin-1-Induced Barrel-Rolling and Other Convulsive Behaviors

The effects of endothelin receptor subtype antagonists on endothelin-1-induced barrel-rolling and convulsive behaviors are shown in Fig. 3 and Table 2. Coadministration of the selective ET_A receptor antagonist BQ-123 (15 nmol/rat, ICV) significantly inhibited the incidence of animals that showed barrel rolling, and the numbers of this behavior produced by endothelin-1 (9 pmol/rat, ICV) ($p < 0.01$). Moreover, the duration of barrel rolling in animals that produced the behavior ($n = 1$) was also reduced compared to that in the endothelin-1-alone group. In contrast, coadministration of the selective ET_B receptor antagonist BQ-788 (15 nmol/rat, ICV) did not modify the endothelin-1–induced barrel-rolling behavior (Fig. 3). In addition, several other convulsive behaviors were also suppressed by the coadministration of BQ-123, but not of BQ-788 (Table 2).

Effects of Endothelin Receptor Subtype Antagonists on the Low-Dose Endothelin-1-Induced Increase in Locomotor Activity

The effects of endothelin receptor subtype antagonists on the low-dose endothelin-1–induced increase in locomotor activity are shown in Fig. 4. Coadministration of BQ-123 (15 nmol/rat, ICV) did not modify the increase in spontaneous locomotor activity produced by low-dose endothelin-1 (1 pmol/rat, ICV). On the other hand, rats that were injected with both BQ-788 (15 nmol) and low-dose endothelin-1 showed spontaneous locomotor activity similar to that in control rats, indicating that BQ-788 abolished the increase in spontaneous locomotor activity produced by a low dose of endothelin-1.

DISCUSSION

The results of the present study on the behavioral effects of endothelin-1 were similar to those in some other previous studies (2,3,8,9,35), especially regarding the convulsive behaviors of rats, including barrel rolling. The first sign we observed

TABLE 1

BEHAVIORAL OBSERVATIONS ON RATS GIVEN VARIOUS INTRAVENTRICULAR DOSES OF ENDOTHELIN-1 (ET-1)

	Treatment			
		ET-1 Doses		
Behavioral Parameters	Saline (9)	1 pmol (12)	3 pmol (11)	9 pmol (15)
Bodily twitching	0	1.3 ± 1.1	1.8 ± 0.4*	2.5 ± 0.2†
Rigidity	0	0.5 ± 0.4	1.7 ± 0.4*	2.4 ± 0.3†
Back crawling	0	0.3 ± 0.2	1.0 ± 0.4	1.3 ± 0.3†
Forepaw dystonia	0	0.1 ± 0.1	1.1 ± 0.4	1.6 ± 0.3†
Hindlimb dystonia	0	0.3 ± 0.3	1.8 ± 0.4*	2.6 ± 0.3†
Fore/hindlimb clonus	0	0.3 ± 0.1	1.6 ± 0.5*	1.8 ± 0.3†
Tail extension	0	0	1.1 ± 0.4	2.2 ± 0.3†
Facial clonus	0	0.7 ± 0.3	0.7 ± 0.4	1.3 ± 0.3†

Behavioral assessments were made on a response scale of 0–3: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. Values were taken during peak response that occurred between 0–30 min after intraventricular injection of saline or drugs. All values are means with SEM for number of rats in parentheses.

* $p < 0.05$,

† $p < 0.01$ vs. saline-treated group.

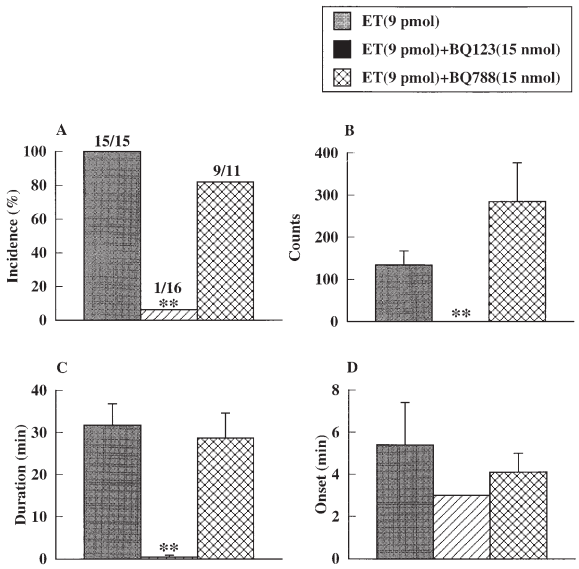

FIG. 3. Effects of BQ-123 (15 nmol/rat, ICV) and BQ-788 (15 nmol/rat, ICV) on barrel rolling. (A) Incidence; (B) counts; (C) duration; (D) onset produced by endothelin-1 (ET; 9 pmol/rat, ICV). Incidence of barrel-rolling behavior (A) was calculated as (positive/total rats) ×100. Each column in D represents the mean ± SEM of positive rats. $^{**}p < 0.01$ vs. ET (9 pmol)-treated group.

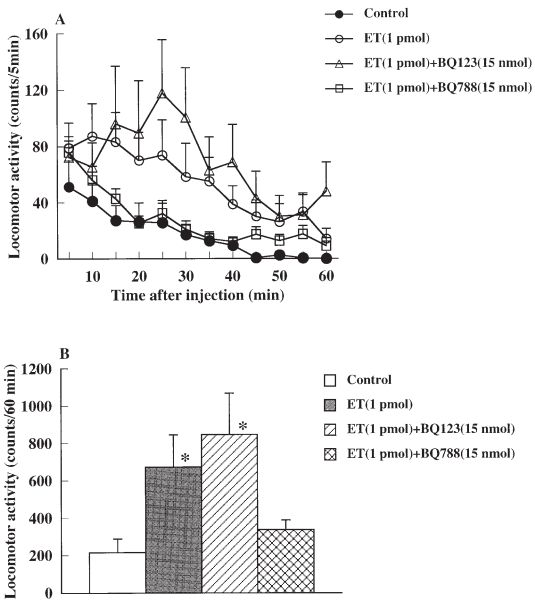

FIG. 4. Time course (A) and total counts (B) of changes in spontaneous locomotor activity produced by endothelin-1 (ET; 1 pmol/rat, ICV) and the effects of BQ-123 (15 nmol/rat, ICV) and BQ-788 (15 nmol/rat, ICV) in rats. Each point and column represents the mean ± SEM of 10–15 rats. $^{*}p < 0.05$ vs. control group.

in rats that had been treated with endothelin-1 was immobilization of the hindquarters followed by static torso twitching. Thereafter, various types of more intense convulsive behaviors, i.e., rigidity, back crawling, fore/hindlimb dystonia, fore/hindlimb clonus, tail extension, and facial clonus, were observed, and this was followed by barrel-rolling behavior. These symptoms that are associated with barrel-rolling behavior appeared at 10 s to 2 or 3 min after the injection of endothelin-1. Because the time to the onset of barrel-rolling behavior was 4 to 5 min after administration, the optimum time for judging whether an individual rat showed barrel-rolling behavior seemed to be 4 to 5 min after administration.

In the present study, we examined whether endothelin-1 produced barrel-rolling and other related convulsive behaviors through the activation of specific endothelin-receptor subtypes, i.e., endothelin ET_A or ET_B receptors. To perform this examination, the selective ET_A antagonist BQ-123 (15) and the selective ET_B receptor antagonist BQ-788 (17) were used. The present study demonstrated that the barrel-rolling behavior produced by ICV administration of endothelin-1 was suppressed by coadministration of the BQ-123, but not of BQ-788. Moreover, other endothelin-1–induced convulsive behaviors were also suppressed by BQ-123, while BQ-788 was ineffective. It has been previously reported that pretreatment

TABLE 2

EFFECTS OF ET_A AND ET_B RECEPTOR ANTAGONISTS ON THE BEHAVIORAL CHENGES PRODUCED BY HIGH DOSE OF ET-1

	Treatment		
Behavioral parameters	ET-1 (9 pmol Alone) (15)	ET-1 (9 pmol) + BQ 123 (15 nmol) (16)	ET-1 (9 pmol) + BQ788 (15 nmol) (11)
Bodily twitching	2.5 ± 0.2	0.3 ± 0.1†	1.8 ± 0.4
Rigidity	2.4 ± 0.3	0†	1.6 ± 0.4
Back crawling	1.3 ± 0.3	0†	1.1 ± 0.5
Forepaw dystonia	1.6 ± 0.3	0†	1.2 ± 0.4
Hindlimb dystonia	2.6 ± 0.3	0.3 ± 0.2†	2.2 ± 0.4
Fore/hindlimb clonus	1.8 ± 0.3	0†	1.5 ± 0.4
Tail extension	2.2 ± 0.3	0†	1.7 ± 0.4
Facial clonus	1.3 ± 0.3	0.6 ± 0.2*	1.2 ± 0.2

Behavioral assessments were made on a response scale of 0–3: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. Values were taken during peak response that occurred between 0–30 min after intraventricular injection of drugs. All valuexs are means with SEM for number of rats in parentheses.

* $p < 0.05$,

† p , 0.01 vs. ET-1 (9 pmol)-treated group.

with the specific ET_A receptor antagonist FR139317 inhibits the barrel-rolling and other convulsive behaviors produced by endothelin-1 (9). This report is consistent with our present findings, and suggests the endothelin-1–induced barrel-rolling and other convulsive behaviors are mediated by mechanisms that involve the ET_A receptor subtype. The location of the ET_A receptors subtypes involved in the expression of convulsive behaviors induced by endothelin-1 are not yet clear. However, glutamatergic neurotransmission, via *N*-methyl-D-aspartate (NMDA) receptor subtypes, has been previously shown to be involved (2,31), and therefore, it is tempting to speculate that endothelin-1 induces convulsive behavior through the activation of ET_A receptors associated with the glutamatergic system.

A noteworthy finding in the present study is that the ICV administration of a low dose of endothelin-1 caused a marked increase in spontaneous locomotor activity. In contrast to barrel-rolling and other convulsive behaviors, this effect of a low dose of endothelin-1 was antagonized by the coadministration of BQ-788, but not of BQ-123. These results suggest that the increase in spontaneous locomotor activity produced by a low dose of ET-1 may occur through a mechanism that involves the ET_B receptor subtype.

Recent neurochemical studies using both in vitro and in vivo methods have suggested the existence of an interaction between endothelin and the dopaminergic system in the central nervous system. In experiments using rat striatal brain slices, it has been found that the application of endothelin-1 or endothelin-3 causes the release of dopamine (21–23), and that this effect was most likely mediated by the ET_B receptor subtype (21). Studies using in vivo microdialysis have also demonstrated that the intrastriatal application of endothelin-1 or endothelin-3 causes the release of dopamine in rats (14,24). A great deal of evidence suggests that an increase in central dopamine neurotransmission is closely involved in the elicitation of motor-activating effects in rodents (20). Based on these previous reports and our present results, we hypothesize that a low dose of endothelin-1 may act at the ET_B receptor subtype to evoke the release of dopamine, and that these effects of endothelin-1 may be involved in the enhancement of spontaneous locomotor activity. Indeed, Webber and van den Buuse (39) reported that contralateral intrastriatal injection of endothelin-1, endothelin-3, or the specific ET_B receptor agonist [$Ala^{1,3,11,15}$]endothelin-1 produced ipsilateral turning behavior in rats with unilateral 6-hydroxydopamine lesions of the nigrostriatal pathway. Pretreatment with BQ-788 or the dopamine D_2 receptor antagonist raclopride blocked the ipsilateral turning response to endothelin-1, while pretreatment with BQ-123 did not inhibit the effect of endothelin-1. This report suggests that changes in dopaminergic neurotransmission mediated by ET_B receptor subtypes are involved in the regulation of locomotor activity and behavior, and supports our present hypothesis.

In conclusion, the results of the present study provide evidence that endothelin-1, which has affinity for both endothelin ET_A and ET_B receptors, acts at central ET_A receptors to evoke barrel-rolling and other convulsive behaviors. In contrast, activation of central ET_B receptors may be involved in the increase in spontaneous locomotor activity produced by a low dose of endothelin-1. This suggests that endothelin receptor subtypes play multiple roles in the regulation of various physiological functions.

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