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β-Phenylethylamine modulates acetylcholine release in the rat striatum: involvement of a dopamine D_2 receptor mechanism

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Abstract

We examined the effects of β-phenylethylamine on striatal acetylcholine release in freely moving rats using in vivo microdialysis. β-Phenylethylamine at 12.5 mg/kg, i.p. did not affect acetylcholine release in the striatum, whereas 25 and 50 mg/kg, i.p. immediately induced an increase in acetylcholine release in the striatum at 15–45 min. This increase following intraperitoneal administration of β-phenylethylamine (25 mg/kg) was not affected by locally applied SCH-23390 (*R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 10 μM), a dopamine D_1 receptor antagonist, nor by raclopride (10 μM), a dopamine D_2 receptor antagonist. The increased release of acetylcholine induced by β-phenylethylamine was suppressed by local infusion of tetrodotoxin (1 μM). In contrast, the extracellular acetylcholine level in the striatum was significantly decreased by local application of β-phenylethylamine (10 and 100 μM) in the striatum via a microdialysis probe. The decrease was completely blocked by local co-application of raclopride (10 μM). The β-phenylethylamine-induced decrease in striatal acetylcholine release was not affected by co-perfusion with SCH-23390 (10 μM). These results indicate that systemic administration of β-phenylethylamine increases acetylcholine release, whereas locally applied β-phenylethylamine decreases striatal acetylcholine release in freely moving rats. Furthermore, the dopaminergic system, through the dopamine D_2 receptor, is involved in the locally applied β-phenylethylamine-induced decrease in acetylcholine in the striatum.

Keywords: Acetylcholine; β-Phenylethylamine; Dopamine receptor antagonist; Microdialysis; Striatum

1. Introduction

β-Phenylethylamine has been detected in the central nervous system of rodents and mammals, and is present in high concentrations in mesolimbic and caudate–putamen structures (Durden et al., 1973; Philips et al., 1978; Reynolds et al., 1980; Paterson et al., 1990). Behavioral studies have demonstrated that β-phenylethylamine induces stereotyped behavior and an enhancement of locomotor activity (Dourish, 1985; Dourish and Boulton, 1981; Dourish et al., 1983). β-Phenylethylamine in the striatum is synthesized in cells containing both tyrosine hydroxylase and aromatic L-amino acid decarboxylase (Dyck et al., 1983; Juorio et al., 1991). Moreover, β-phenylethylamine stimulates the release of dopamine in the striatum (Dyck et al., 1983; Bailey et al., 1987) and the nucleus accumbens (Barroso and Rodriguez, 1996; Nakamura et al., 1998). Thus, it regulates catecholaminergic neurotransmitter release, and this regulation is especially predominant in dopaminergic neurons. In addition, a study involving an in vitro model with striatal slices showed that β-phenylethylamine inhibits the electrically induced release of [^{3}H]acetylcholine (Baud et al., 1985). Therefore, the effect of β-phenylethylamine appears in response to modification of acetylcholine release through dopaminergic neurotransmission.

Nigrostriatal dopaminergic neurons regulate acetylcholine release via dopamine D_1 and D_2 receptors. Systemic administration of a dopamine D_2 receptor agonist decreases the release of acetylcholine, whereas a dopamine D_1 receptor agonist significantly increases acetylcholine release in the striatum (Damsma et al., 1990; Hagiwara et al., 1993; De Boer and Abercrombie, 1996; Acquas et al.,

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1997). Previous research has demonstrated that intrastriatal infusion of a dopamine D_1 receptor agonist produces an increase in acetylcholine release (Ajima et al., 1990; Zocchi and Pert, 1993). Thus, increasing evidence suggests that a close functional relationship exists between the dopaminergic system and the release of acetylcholine in the striatum. Therefore, acetylcholine release in the striatum may play a role in the psychopharmacological effect produced by β-phenylethylamine, but it remains to be determined whether β-phenylethylamine affects the release of acetylcholine in the striatum of freely moving rats.

The present study assessed the effects of β-phenylethylamine on acetylcholine release in the striatum through the use of in vivo microdialysis. We also investigated whether the dopamine D_1 and D_2 receptors alter the effect of systemically or locally applied β-phenylethylamine on the release of acetylcholine in the striatum.

2. Materials and methods

2.1. Surgical procedures

Male Wistar rats weighing 270–340 g were used in these experiments. Sixty rats were anesthetized with pentobarbital–Na (40 mg/kg, i.p.) and positioned in a stereotaxic apparatus. The rat's skull was exposed and drilled to allow for implantation of a guide cannula into the upper part (3.0 mm) of the striatum (bregma: +0.3 mm, lateral: 3.0 mm, depth: 3.0 mm; Paxinos and Watson, 1986). The guide cannula was held firmly in place by dental acrylic cement and anchored to the skull using stainless steel screws. All experiments were performed 3 days after surgery.

2.2. In vivo microdialysis

Microdialysis probes (dialysis membrane: length 3.0 mm, diameter 0.5 mm, AF-03; Eicom, Kyoto, Japan) were inserted into the striatum through the previously implanted guide cannula. The animals were placed in a Plexiglas cage (30 cm × 30 cm × 38 cm) and were connected by polyethylene inflow and outflow tubes to a syringe pump (CMA 100; Carnegie Medicin) and collection vials. Perfusion solution (125 mM NaCl, 3 mM KCl, 1.3 mM $CaCl_2$, 1 mM $MgCl_2$ and 23 mM $NaHCO_3$) in aqueous potassium phosphate buffer (1 mM, pH 7.4) containing neostigmine (100 nM) was perfused into the dialysis probe at a rate of 2 μl/min. The perfusate was collected at 15-min intervals. Acetylcholine in each perfusate was quantitatively measured using high-performance liquid chromatography with electrochemical detection (HPLC-ECD), as described previously (Taguchi et al., 1999). The system consisted of a pump (EP-300; Eicom), separating column (Eicompak AC-GEL, 2.0 × 150 mm), enzymatic reactor (AC-Enzypak; Eicom) and electrochemical detector (ECD-300; Eicom). Acetylcholine was converted into choline and then hydrogen peroxide with an enzyme reactor containing acetylcholine esterase and choline oxidase, which was detected electrochemically. The mobile phase consisted of 0.05 M phosphate buffer (pH 8.2) containing 300 mg/l sodium 1-decanesulfonate and 5 mg/l EDTA–2Na delivered at a constant flow rate of 0.15 ml/min using an HPLC pump. The column temperature was maintained at 33°C.

2.3. Materials

β-Phenylethylamine hydrochloride, purchased from Tokyo Chemical Industry (Tokyo, Japan), was dissolved in physiological saline for intraperitoneal administration. (+)-SCH-23390 [*R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine] hydrochloride and *S*(−)-raclopride-L-tartrate were from Research Biochemicals International (Natick, MA, USA), and tetrodotoxin was purchased from Wako (Osaka, Japan).

All drugs were dissolved in perfusion solution for intrastriatal application through the dialysis probe, and each solution was sterilized prior to application by filtration through a Millipore filter (0.20 μm). All analytical grade chemicals used for perfusion and the mobile phase were from Tokyo Chemical Industry or Wako.

2.4. Data evaluation

Data are shown as the means ± S.E.M. of the percentage of the baseline level for each rat as determined prior to drug application. Statistical significance was analyzed by one- or two-way repeated-measures analysis of variance (RM-ANOVA), followed by Dunnett's multiple comparison test or by a non-paired *t*-test. Differences were considered significant when the P value was less than 0.05.

3. Results

3.1. Effect of systemic administration of β-phenylethylamine on striatal acetylcholine release

The amount of extracellular acetylcholine recovered from the striatum with chronically implanted microdialysis probes was 269.0 ± 22.9 fmol/30 μl ($n = 60$). The basal release of acetylcholine was stable for 4 h after the start of perfusion of a solution containing 100 nM neostigmine.

As shown in Fig. 1, β-phenylethylamine (12.5, 25 and 50 mg/kg, i.p.) increased acetylcholine release in the striatum (two-way RM-ANOVA; Treatment × Time interaction: $F(30,132) = 1.736$, $P = 0.008$). At a dose of 12.5 mg/kg, β-phenylethylamine induced a slight increase in acetylcholine release at 15 min compared with saline, although this increase was not significant according to

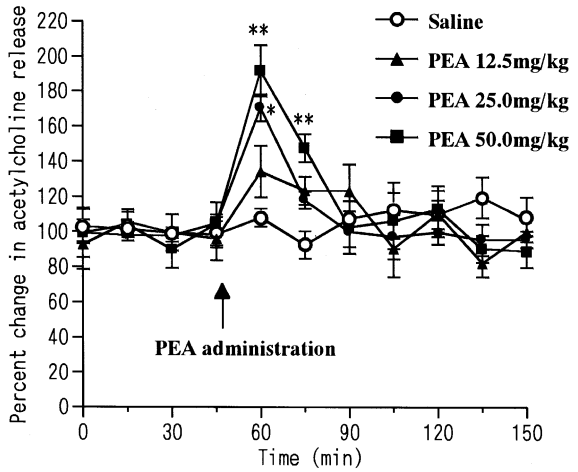

Fig. 1. Effects of systemic administration of β-phenylethylamine (PEA) on the release of acetylcholine in the striatum. β-Phenylethylamine was administered intraperitoneally at doses of 12.5 (closed triangle), 25.0 (closed circle) and 50.0 mg/kg (closed square). β-Phenylethylamine significantly increased the release of acetylcholine [two-way RM-ANOVA; Treatment × Time interaction: $F(30,132) = 1.736$, $P = 0.008$]. Asterisks indicate significant differences compared to the saline group (open circle) at $^{*}P < 0.05$ or $^{**}P < 0.01$ by Dunnett's multiple comparison test.

Dunnett's test. At a dose of 25 mg/kg, β-phenylethylamine significantly increased the release of acetylcholine by 70.5 ± 7.7% (Dunnett's test; $P < 0.05$ vs. saline, $n = 4$) at 15 min. Systemic administration of β-phenylethylamine (50 mg/kg) increased acetylcholine release, with release peaking at 91.8 ± 10.8% (Dunnett's test; $P < 0.01$ vs. saline, $n = 4$) at 15 min. A significant increase in acetylcholine release was also observed 30 min after β-phenylethylamine injection (Dunnett's test; $P < 0.01$ vs. saline). Recovery was observed 45 min later. Intraperitoneal administration of β-phenylethylamine dose-dependently increased acetylcholine release in the striatum.

3.2. Effect of systemic administration of β-phenylethylamine on behavioral responses

Systemic administration of β-phenylethylamine (12.5 mg/kg) had no behavioral effect. However, a higher dose of β-phenylethylamine (25 and 50 mg/kg) increased locomotor activity, rearing and sniffing at 10–15 min after injection. β-phenylethylamine at a dose of 50 mg/kg elicited stereotyped head movements.

3.3. Effects of locally applied tetrodotoxin on systemic β-phenylethylamine-induced striatal acetylcholine release

We examined the effect of pretreatment with 1 μM tetrodotoxin (Na^+ channel blocker) on acetylcholine release in the striatum induced by systemic administration of β-phenylethylamine (25 mg/kg, i.p). Intrastriatal infusion of tetrodotoxin reduced the baseline levels of striatal acetylcholine release (one-way RM-ANOVA; $F(12,36) = 55.720$, $P < 0.001$; Fig. 2). As shown in Fig. 2, local application of tetrodotoxin 30 min before systemic administration of β-phenylethylamine (25 mg/kg, $n = 4$) suppressed the β-phenylethylamine-induced increase in acetylcholine release in the striatum.

3.4. Effects of locally applied dopamine receptor antagonists on systemic β-phenylethylamine-induced striatal acetylcholine release

We then examined the effects of locally applied SCH-23390 (dopamine D_1 receptor antagonist) and raclopride (dopamine D_2 receptor antagonist) on acetylcholine release in the striatum. Intrastriatal infusion of raclopride (10 μM) significantly increased basal acetylcholine release by 60.7 ± 7.3% (one-way RM-ANOVA; $F(12,36) = 7.836$, $P < 0.001$, $n = 4$; Fig. 3A), while SCH-23390 had no significant effect (one-way RM-ANOVA; $F(12,36) = 0.813$, $P = 0.635$, $n = 4$; Fig. 3B). Systemic administration of β-phenylethylamine (25 mg/kg) significantly increased acetylcholine release when SCH-23390 (10 μM) was applied in the striatum (two-way RM-ANOVA; Treatment × Time interaction: $F(12,78) = 5.367$, $P < 0.001$, $n = 4$; Fig. 3A). This increase was still observed 30 min after β-phenylethylamine administration (non-paired *t*-test, $P < 0.05$). Systemic administration of β-phenylethylamine (25 mg/kg) also significantly increased acetylcholine release when raclopride (10 μM) was applied in the striatum (two-way RM-ANOVA; Treatment × Time interaction: $F(12,78) = 2.506$, $P = 0.008$, $n = 4$; Fig. 3B). This increase was observed at 15 min after β-phenylethylamine administration (non-paired *t*-test, $P < 0.05$). SCH-23390 and raclopride did not affect the systemic β-phenylethylamine-induced increase in acetylcholine release.

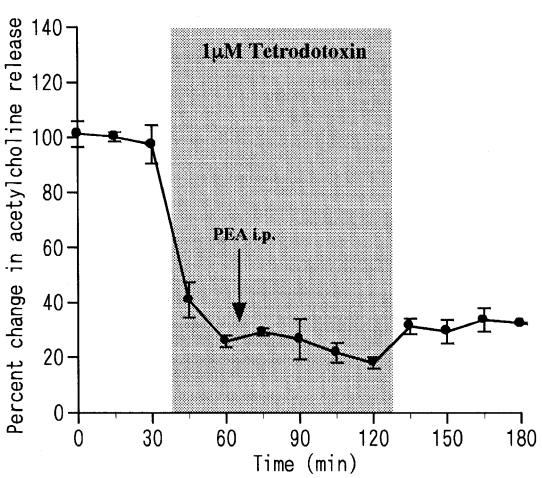

Fig. 2. Effects of tetrodotoxin on the release of acetylcholine in the striatum. Tetrodotoxin (1 μM) locally applied into the striatum reduced the release of acetylcholine [one-way RM-ANOVA; $F(12,36) = 55.720$, $P < 0.001$] and blocked the β-phenylethylamine (PEA, 25 mg/kg)-induced increase in acetylcholine release.

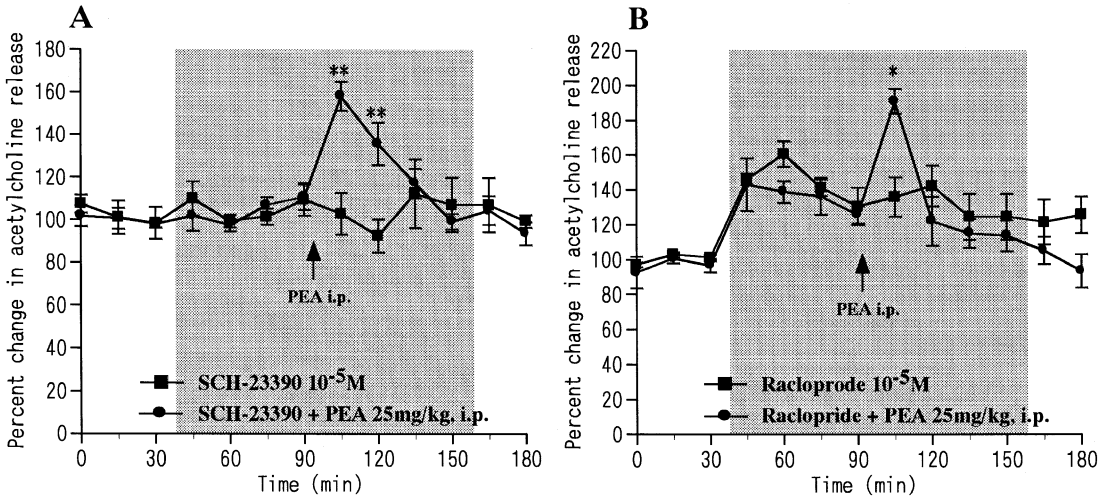

Fig. 3. Effects of dopamine receptor antagonists on the β-phenylethylamine (PEA, 25 mg/kg)-stimulated release of acetylcholine in the striatum. (A) SCH-23390 (10 μM), a dopamine D_1 receptor antagonist, was locally applied in the striatum (shadowed area). β-Phenylethylamine (open circle) significantly increased the release of acetylcholine when SCH-23390 was infused with perfusion solution [two-way RM-ANOVA; interaction: $F(12,78) = 5.367$, $P < 0.001$, $n = 4$]. (B) Raclopride (10 μM), a dopamine D_2 receptor antagonist, locally applied in the striatum (shadowed area), significantly increased basal acetylcholine release [one-way RM-ANOVA; $F(12,36) = 7.836$, $P < 0.001$, $n = 4$]. β-Phenylethylamine significantly increased the release of acetylcholine when raclopride was infused with perfusion solution [two-way RM-ANOVA; interaction: $F(12,78) = 2.506$, $P = 0.008$, $n = 4$]. Asterisks indicate significant differences at $^{*}P < 0.05$ or $^{**}P < 0.01$ by non-paired *t*-test.

3.5. Effect of locally applied β-phenylethylamine on striatal acetylcholine release

We next examined the effects of locally applied β-phenylethylamine (1, 10 and 100 μM) on acetylcholine release in the striatum (Fig. 4). β-Phenylethylamine (1 μM) slightly reduced the release of acetylcholine in the striatum, but not significantly (one-way RM-ANOVA; $F(11,44) = 1.566$, $P = 0.143$, $n = 5$). Local application of β-phenylethylamine (10 μM) significantly decreased the release of acetylcholine by 29.6 ± 8.2% at 30 min (one-way RM-ANOVA; $F(11,44) = 3.416$, $P = 0.002$, $n = 5$). At 100 μM, it also significantly decreased acetylcholine release by 15.8 ± 10.3% at 15 min, with a maximum decrease in release of 47.2 ± 11.6% observed at 30 min (one-way RM-ANOVA; $F(11,44) = 5.724$, $P < 0.001$, $n = 5$). The decrease in acetylcholine release was reversed after removal of β-phenylethylamine from the perfusate.

3.6. Effects of locally co-applied dopamine receptor antagonists with β-phenylethylamine on striatal acetylcholine release

Finally, we examined the effects of local co-application of SCH-23390 or raclopride with β-phenylethylamine on acetylcholine release in the striatum (Fig. 5A,B).

A reduction in acetylcholine release induced by β-phenylethylamine was also observed when SCH-23390 was applied in the striatum 60 min before β-phenylethylamine application (two-way RM-ANOVA; Treatment × Time interaction: $F(14,90) = 3.629$, $P < 0.001$, $n = 4$; Fig. 5A). Locally applied β-phenylethylamine also significantly reduced acetylcholine release (non-paired *t*-test, $P < 0.05$). In contrast, local application of raclopride (10 μM) at 60 min before co-administration with β-phenylethylamine blocked the β-phenylethylamine-induced decrease in acetylcholine release (two-way RM-ANOVA; Treatment:

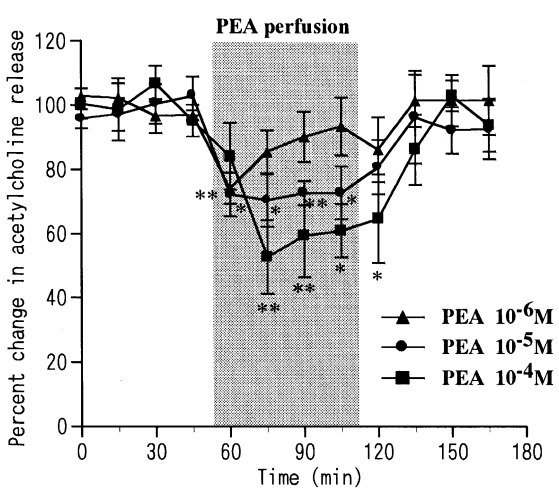

Fig. 4. Effect of locally applied β-phenylethylamine (PEA) on striatal acetylcholine release. β-Phenylethylamine [10^{-6} M (closed triangle), 10^{-5} M (closed circle) and 10^{-4} M (closed square)] was applied in the striatum through the dialysis probe. β-Phenylethylamine significantly reduced the release of acetylcholine [one-way RM-ANOVA; 10^{-5} M: $F(11,44) = 3.416$, $P = 0.002$, $n = 5$; 10^{-4} M: $F(11,44) = 5.724$, $P < 0.001$, $n = 5$). Asterisks indicate significant differences between most recent basal values and each subsequent value at $^{*}P < 0.05$ or $^{**}P < 0.01$ by Dunnett's multiple comparison test.

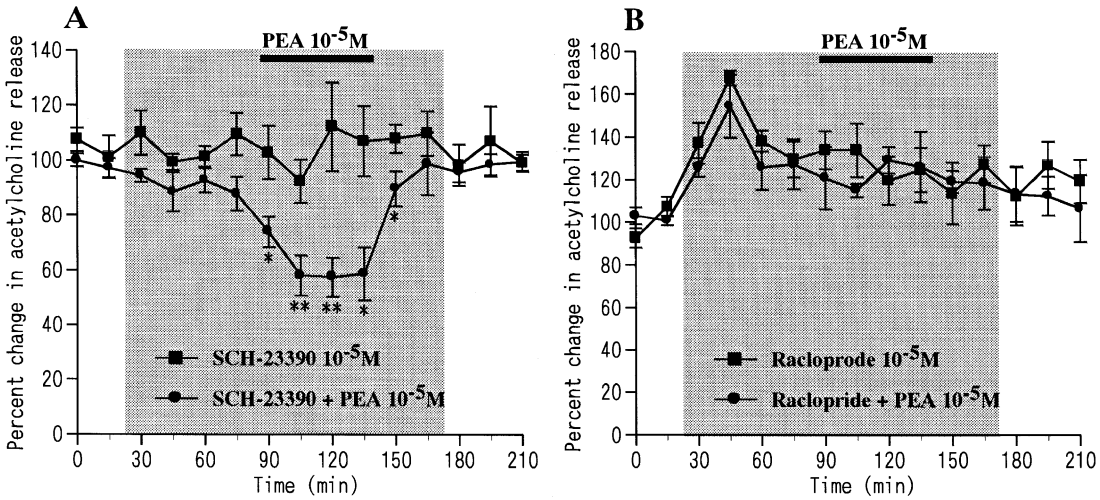

Fig. 5. Effects of dopamine receptor antagonists on locally applied β-phenylethylamine (PEA, 10^{-5} M)-induced reduction of acetylcholine release in the striatum. (A) SCH-23390 (10 μM), a dopamine D_1 receptor antagonist, was applied in the striatum (shadowed area). β-Phenylethylamine significantly decreased the release of acetylcholine when SCH-23390 was co-applied with β-phenylethylamine [two-way RM-ANOVA; interaction: $F(14,90) = 3.629$, $P < 0.001$, $n = 4$]. (B) Raclopride (10 μM), a dopamine D_2 receptor antagonist, was locally applied in the striatum (shadowed area). Decreased release of acetylcholine induced by β-phenylethylamine was blocked by raclopride [two-way RM-ANOVA; Treatment: $F(1,120) = 3.015$, $P = 0.085$; Time: $F(14,120) = 4.206$, $P < 0.001$; interaction: $F(14,120) = 0.485$, $P = 0.938$, $n = 5$, open circle]. Asterisks indicate significant differences at $^{*}P < 0.05$ or $^{**}P < 0.01$ by non-paired *t*-test.

$F(1,120) = 3.015$, $P = 0.085$; Time: $F(14,120) = 4.206$, $P < 0.001$; Treatment × Time interaction: $F(14,120) = 0.485$, $P = 0.938$, $n = 5$; Fig. 5B).

4. Discussion

Like amphetamines, the trace amine, β-phenylethylamine, increases the release of dopamine in the striatum (Raiteri et al., 1977; Philips and Robson, 1983; Bailey et al., 1987). Researchers have postulated that β-phenylethylamine acts as a co-transmitter or neuromodulator of catecholaminergic neurotransmission (Paterson et al., 1990; Nakamura et al., 1998). Our in vivo microdialysis findings indicate that intraperitoneal administration of β-phenylethylamine increases the release of acetylcholine in the rat striatum. In addition, amphetamine and methamphetamine have been shown to increase the release of acetylcholine in the striatum of the rat (Mandel et al., 1994; Acquas et al., 1997; Taguchi et al,, 1998). The results of these studies suggest that psychomotor stimulants enhance cholinergic activity in the striatum of freely moving rats.

It has been demonstrated by in vivo microdialysis that the release of acetylcholine in the striatum is regulated by the nigrostriatal dopaminergic system (Ajima et al., 1990; Bertorelli and Consolo, 1990; De Boer and Abercrombie, 1996). These results suggest that dopamine D_1 and dopamine D_2 receptors exert opposite effects on striatal acetylcholine release. However, Acquas et al. (1997) demonstrated that striatal infusion of dopamine D_1 receptor agonists and antagonists does not affect acetylcholine release, and that dopamine D_1 receptors are not located in the striatum. In the present experiments, SCH-23390 (dopamine D_1 receptor antagonist) and raclopride (dopamine D_2 receptor antagonist) had no effect on the increase in acetylcholine release in the striatum induced by systemic administration of β-phenylethylamine. These results suggest that the dopamine receptor is not involved in the effect of β-phenylethylamine on the release of acetylcholine. Thus, it appears unlikely that the increase in acetylcholine release induced by systemic administration of β-phenylethylamine is primarily due to the nigrostriatal dopaminergic system involved in dopamine release. However, dopamine D_1 receptor antagonists attenuate the amphetamine-induced increase in striatal acetylcholine release at a low neostigmine concentration (10 nM) (De Boer and Abercrombie, 1996).

The striatum is known to receive varying types of neuronal innervations from other brain regions, such as the cortex and thalamic nuclei, which are functionally connected to the striatum (Cooper et al., 1991). The acetylcholine release induced by β-phenylethylamine is likely mediated by other neurotransmitters released in the striatum. The effects of β-phenylethylamine are known to be mediated by the noradrenergic, serotonergic, glutaminergic and opiate systems in the central nervous system (Garzon et al., 1980; Sloviter et al., 1980; Taguchi et al., 1990; Consolo et al., 1996). In our study, the increase in acetylcholine release caused by systemic administration of β-phenylethylamine appeared to be dependent on neuronal activity, since pretreatment with tetrodotoxin, an agent that blocks voltage-dependent Na^+ channels, completely suppressed the systemic β-phenylethylamine-induced increase in acetylcholine release. Thus, the effect of β-phenylethyl-

amine on the striatum is likely due to the neuronal release of acetylcholine. Taken together, these findings suggest that systemic administration of β-phenylethylamine regulates acetylcholine release in the striatum via an extrastriatal origin.

Acetylcholinesterase inhibitors may significantly modulate the effect of psychomotor stimulants on striatal acetylcholine release. Systemic administration of amphetamine was found to increase acetylcholine release when perfusion solution containing neostigmine (100 nM) was used (Damsma et al., 1991; Acquas and Fibiger, 1998). In contrast, amphetamine significantly decreased the release of acetylcholine in the striatum in the absence of a cholinesterase inhibitor (De Boer and Abercrombie, 1996). Thus, striatal acetylcholine release, as evaluated by in vivo microdialysis, may be under the control of a complex relationship between psychomotor stimulants and cholinesterase inhibition.

Locally applied β-phenylethylamine might act more directly on acetylcholine release by cholinergic interneurons in the striatum. Iontophoretically applied β-phenylethylamine may act post-synaptically to potentiate the cortical neuron response to microiontophoretically applied norepinephrine (Paterson and Boulton, 1988) and the caudate nucleus neuron response to microiontophoretically applied dopamine (Paterson et al., 1990). In the present study, β-phenylethylamine administration decreased the release of acetylcholine in the striatum. Moreover, local infusion of β-phenylethylamine decreased the extracellular striatal acetylcholine concentration in a dose-dependent manner. Thus, trace amines, such as β-phenylethylamine, directly cause a decrease in striatal acetylcholine release. However, β-phenylethylamine increases the levels of dopamine in the striatum (Dyck et al., 1983; Bailey et al., 1987). We investigated whether the decrease in acetylcholine release induced by intrastriatal application of β-phenylethylamine was dependent on the dopaminergic system. The decrease induced by intrastriatal infusion of β-phenylethylamine (10 μM) was blocked when the dopamine D_2 receptor antagonist, raclopride, was co-perfused into the striatum. In contrast, the β-phenylethylamine (10 μM)-induced decrease was not affected by co-application of SCH-23390, a dopamine D_1 receptor antagonist. The present results suggested that the decrease in acetylcholine release induced by local application of β-phenylethylamine was affected by binding to dopamine D_2 receptors in the striatum.

Our results suggest that systemic β-phenylethylamine and intrastriatal infusion of β-phenylethylamine exert opposite effects on striatal acetylcholine release. Thus, a comparison of acetylcholine release from the striatum in response to systemic administration and local application of β-phenylethylamine suggested that the systemic β-phenylethylamine-induced increase in acetylcholine release was not mediated at the level of the striatum but through another system at a site outside the striatum. It is likely that the systemic β-phenylethylamine-induced increase in striatal acetylcholine release blocked the decreasing effect of local application of β-phenylethylamine, although relatively high concentrations of β-phenylethylamine are found in the striatum compared to other central nervous system areas after systemic administration of β-phenylethylamine (Durden et al., 1973; Philips et al., 1978; Reynolds et al., 1980; Paterson et al., 1990). Moreover, the effect of systemic administration of psychomotor stimulants is not always the same as that of local application of the corresponding agent (De Boer et al., 1992; Mandel et al., 1994; Acquas and Fibiger, 1998). Thus, systemic β-phenylethylamine may mainly exert its effect via an extrastriatal mechanisms.

We conclude that systemic administration of β-phenylethylamine increases acetylcholine release in the striatum in freely moving rats, and that the dopamine D_2 receptor is involved in the effect of local application of β-phenylethylamine on the release of acetylcholine.

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