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The effect of methamphetamine on the release of acetylcholine in the rat striatum

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Abstract

We examined the effect of methamphetamine on the release of acetylcholine in the striatum of freely moving rats, using an in vivo microdialysis method. The basal level of acetylcholine was 3.67 ± 0.47 pmol/30 μl per 15 min in the presence of neostigmine (10 μM). Tetrodotoxin (1 μM), a selective blocker of voltage-dependent Na^+ channels, markedly inhibited the release of acetylcholine in the striatal perfusates. Apomorphine (1.0 mg/kg, i.p.), a dopamine receptor agonist, also significantly attenuated acetylcholine release. Methamphetamine (0.1 and 0.5 mg/kg, i.p.) did not immediately affect acetylcholine release in the striatum, but a dose of 1.0 mg/kg (i.p.) induced an increase of acetylcholine release in the striatum at 15–60 min. Striatal infusion of methamphetamine (5 and 10 μM) did not influence acetylcholine release. The increase following intraperitoneal administration of methamphetamine was slightly diminished by haloperidol (0.5 mg/kg). After microinjection of the neurotoxin, 6-hydroxydopamine (6 μg/3 μl), in the substantia nigra 7 days before, the increase of acetylcholine induced by the administration of methamphetamine (1.0 mg/kg) was slightly attenuated, whereas the administration of reserpine (2 mg/kg, i.p.) 24 h before, combined with α-methyl-*p*-tyrosine (300 mg/kg, i.p.) 2.5 h before, completely blocked the increase in release of acetylcholine. These findings suggest that methamphetamine exerts an excitatory influence on striatal acetylcholine release in freely moving rats, and that this excitatory effect involves the dopaminergic system and the catecholaminergic system.

Keywords: Acetylcholine; Methamphetamine; Dopaminergic system; Striatum; Microdialysis, in vivo; Microdialysis, in vitro

1. Introduction

Release of acetylcholine induced by psychomotor stimulants such as amphetamine and methamphetamine has been demonstrated in in vivo and in vitro experiments (DeBelleroche et al., 1982; Baud et al., 1985; DeBoer et al., 1990; Florin et al., 1992). In an in vitro model with striatal slices, it was shown that amphetamine inhibits the electrically induced release of [^{3}H]acetylcholine when endogenous levels of dopamine depleted by treatment with the neurotoxin, 6-hydroxydopamine, or with reserpine (Cantrill et al., 1983; Baud et al., 1985). In addition, amphetamine was shown to inhibit the electrically induced [^{3}H]acetylcholine release in rabbit striatal slices in a concentration-dependent manner (Parker and Cubeddu, 1986). In an in vivo experiment, amphetamine increased acetylcholine release in the striatum of freely moving rats (Florin et al., 1992; Guix et al., 1992; Cadoni et al., 1995). Mandel et al. (1994) reported similar results following systemic administration of amphetamine to anesthetized rats, and indicated that amphetamine-induced striatal acetylcholine release was not dependent on the nigrostriatal dopaminergic system. However, Damsma et al. (1991) demonstrated that amphetamine increased acetylcholine release in the striatum via a dopamine D_1 receptor mechanism. In addition, methamphetamine induced a significant increase in acetylcholine release in the frontal cortex, and this effect was completely inhibited by co-administration of the dopamine receptor antagonist, haloperidol (Okada, 1991). Thus, amphetamine-like compounds appear to exert contradictory effects on acetylcholine release via the dopaminergic system.

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The influence of amphetamine and methamphetamine on dopaminergic transmission in the brain is well known. Many studies have shown that amphetamine and methamphetamine release catecholamines from newly synthesized cytosolic pools, and that the effects of these drugs can be blocked by the inhibition of catecholamine synthesis by the administration of α-methyl-*p*-tyrosine (Scheel-Krüger, 1971; Parker and Cubeddu, 1986; Butcher et al., 1988). Moreover, methamphetamine causes the release of dopamine and norepinephrine from monoamine-containing neurons (Raiteri et al., 1979). Recently, it was shown, using in vivo microdialysis, that the release of acetylcholine from the striatum is regulated by dopamine D_1 or D_2 receptor agonists (Ajima et al., 1990; Damsma et al., 1990; DeBoer and Abercrombie, 1996). Thus, several findings indicate a close functional relationship between the dopaminergic system and the release of acetylcholine in the striatum.

In the present study, the effects of methamphetamine on acetylcholine release in the striatum were assessed using in vivo microdialysis. We also investigated whether the nigrostriatal dopaminergic system is involved with the influence of methamphetamine on the release of acetylcholine from the striatum.

2. Materials and methods

Forty-five adult male Wistar rats (240–280 g) were anesthetized with pentobarbital sodium (50 mg/kg, i.p.) and positioned in a stereotaxic apparatus. In each rat the skull was exposed, and a hole was drilled for a microdialysis probe (CMA 10, Carnegie Medicin; diameter 0.5 mm, dialysis membrane 3.0 mm; mol/wt. cut-off 20,000) which was implanted into the striatum (bregma: +0.2, lateral: 2.0 to 3.0, ventral: −5.5 to −6.0, Paxinos and Watson, 1986). All experiments were performed 48 h after surgery. 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.

Ringer solution (147 mM NaCl, 4 mM KCl and 3.4 mM $CaCl_2$) containing neostigmine (10 μM) was perfused into the dialysis probe at a rate of 2 μl/min. The perfusate was collected at 15 min intervals. Acetylcholine was measured by high-performance liquid chromatography (HPLC) using electrochemical detection (ECD), as described previously (Taguchi et al., 1993). The HPLC-ECD system included a pump (PM-60, BAS), guard and chromatographic column (5 × 4 mm and 2 × 110 mm, BAS) and ECD (LC-4B, BAS). The mobile phase (pH 8.4) consisted of 50 mM Na_2HPO_4, 0.5 mM EDTA 2 Na, and 0.45 mM sodium octanesulfonate. The applied potential at the working electrode was +450 mV (vs. Ag/AgCl). Both the chromatographic column and enzyme reactor column were maintained at 37°C using a column heater (LC-22A, BAS).

The following experimental groups were studied. (1) Under control conditions, the experiment was performed using untreated rats. (2) Tetrodotoxin (1 μM) and methamphetamine (5 and 10 μM) were dissolved in neostigmine-containing Ringer's solution and perfused into the striatum through the dialysis tube for 60 min using a liquid switch (Carnegie Medicin). (3) Rats were pretreated with reserpine (2.0 mg/kg, s.c.), 24 h before the experiment, in combination with α-methyl-*p*-tyrosine (300 mg/kg, i.p.) 2.5 h before the experiment. (4) Rats were anesthetized with pentobarbital-Na (50 mg/kg, i.p.), and an unilateral lesion of the substantia nigra (bregma: −5.2, lateral: 2.0, ventral: −5.0 to −5.5: Paxinos and Watson, 1986) was created by stereotaxic infusion at a rate of 3 μl/3 min of a solution of 6-hydroxydopamine plus 0.1% ascorbic acid. The solution contained 6 μg of 6-hydroxydopamine base dissolved in 0.9% saline. The experiments were performed 1 week after the administration of 6-hydroxydopamine. Effects in reserpine plus α-methyl-*p*-tyrosine-treated rats and 6-hydroxydopamine-treated rats were evaluated by measurement of dopamine, homovanillic acid and 3,4-dihydroxyphenyl acetic acid in the striatum using in vivo microdialysis (Ungerstedt, 1984). Only rats showing > 80% depletion of dopamine, homovanillic acid and 3,4-dihydroxyphenyl acetic acid in the dialysate were used for the experiments. After the end of the experiments, the animals were killed with an overdose of pentobarbital-Na. The brain was fixed in 10% formalin. Frozen 100 μm thick sections were cut using a freezing microtome. The tracks of the dialysis cannula were verified microscopically in the histological sections.

The data were analyzed statistically using Dunnett's multiple comparison test and Student's *t*-test (non-paired). Differences were considered significant when P values were less than 0.05.

The drugs used were methamphetamine (Dainippon Seiyaku), tetrodotoxin (Sigma), 6-hydroxydopamine (Sigma), α-methyl-*p*-tyrosine (Sigma), apomorphine (Sigma), and haloperidol (Dainippon Seikaku). Drugs for injection were dissolved in 0.9% saline. Apomorphine was dissolved in saline plus 0.1 mg/ml ascorbic acid.

3. Results

3.1. Effects of tetrodotoxin and apomorphine on acetylcholine release

The acetylcholine level in three control samples taken before drug injection was 3.67 ± 0.47 pmol/15 min in 30 μl of striatal perfusate. The basal release of acetylcholine was stable for 3 h after the initiation of perfusion with Ringer's solution (containing 10 μM of neostigmine). Ringer's solution containing 1 μM tetrodotoxin was infused for 60 min. Tetrodotoxin inhibited the release of acetylcholine in rat striatum by 85.3 ± 9.5% ($P < 0.01$) at

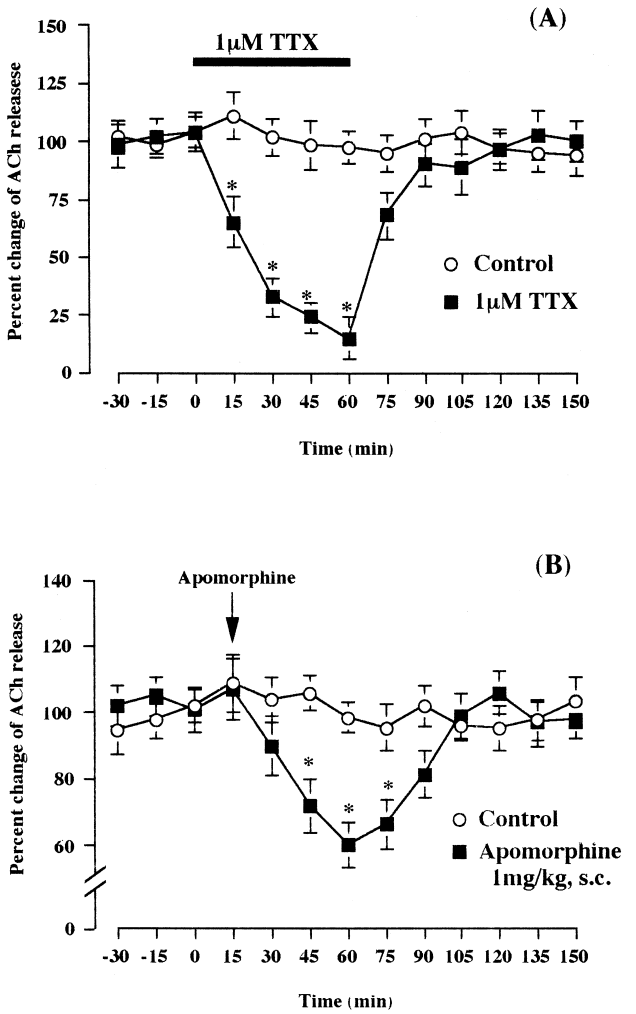

Fig. 1. (A) Effects of perfusion of tetrodotoxin (1 μM) on acetylcholine release in the rat striatum. Tetrodotoxin was perfused for 60 min by inclusion in Ringer's solution. Basal value 3.67 ± 0.47 pmol/15 min per 30 μl. Each point represents the mean ± S.E.M., and asterisks indicate a significant difference (* $P < 0.01$) between saline group (open circles, $n = 5$) and tetrodotoxin-treated groups (closed squares, $n = 6$). (B) Effects of apomorphine on extracellular acetylcholine release in the rat striatum. Apomorphine (1.0 mg/kg, s.c.) reduced the level of acetylcholine from 3.60 ± 0.54 to 2.15 ± 0.84 pmol/15 min at 60 min. Each point represents the mean ± S.E.M., and asterisks indicate a significant difference (* $P < 0.01$) between saline group (open circles, $n = 5$) and apomorphine-treated groups (closed squares, $n = 6$).

60 min (Fig. 1A). Upon the removal of tetrodotoxin, the acetylcholine levels gradually returned towards their basal level. Subcutaneous apomorphine (1.0 mg/kg) decreased the release of striatal acetylcholine at 60 min by 40.3 ± 6.1% ($P < 0.01$) (Fig. 1B). Recovery was observed 105 min later.

3.2. Effects of methamphetamine on acetylcholine release in untreated rats

Fig. 2A shows the effects of methamphetamine (0.1, 0.5 and 1.0 mg/kg, i.p.) on the release of acetylcholine in the striatum. At a dose of 0.5 mg/kg, methamphetamine induced a slight increase of acetylcholine release (15.4 ± 9.0%) in comparison with that in the saline group (Fig. 2A). At a dose of 1.0 mg/kg, methamphetamine significantly increased the release of striatal acetylcholine by 28.8 ± 4.2% ($P < 0.05$) at 15 min, and the effect peaked

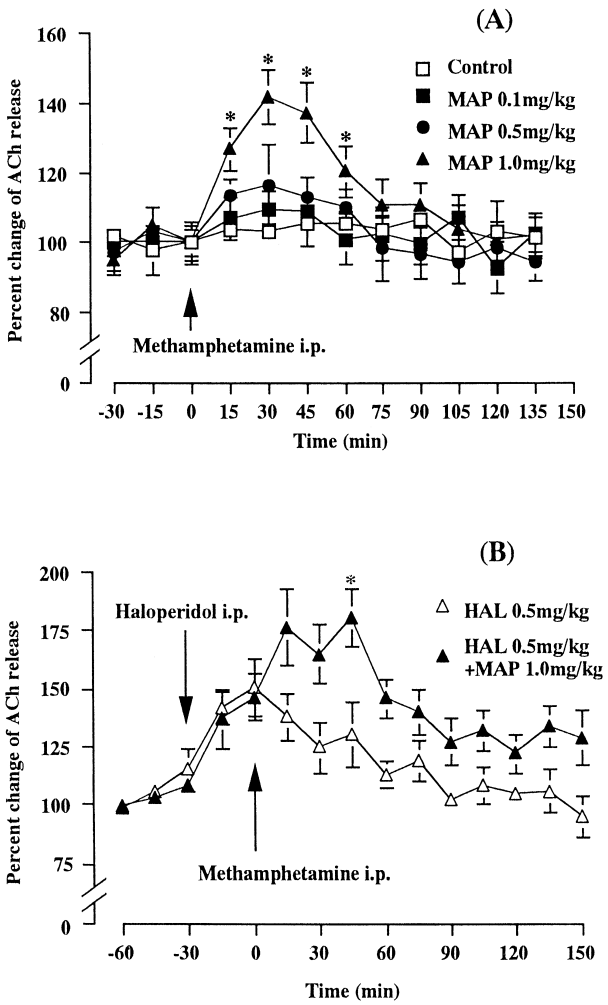

Fig. 2. (A) Effects of methamphetamine on extracellular acetylcholine release in the rat striatum. Methamphetamine (1.0 mg/kg, i.p.) increased the release of acetylcholine from 3.59 ± 0.54 to 5.13 ± 0.54 pmol/15 min at 30 min. Each point represents the mean ± S.E.M., and asterisks indicate a significant difference (* $P < 0.01$) between saline group and methamphetamine-treated groups. Methamphetamine (closed squares, 0.1 mg/kg, $n = 5$; closed circles, 0.5 mg/kg, $n = 6$; closed triangles, 1.0 mg/kg, $n = 5$); saline (open squares, 1.0 ml/kg, $n = 5$). (B) Effects of methamphetamine and haloperidol on extracellular acetylcholine release in the rat striatum. Haloperidol (0.5 mg/kg, i.p.) administered 30 min before methamphetamine (1.0 mg/kg), attenuated the methamphetamine-induced increase of acetylcholine release at 30 and 45 min. Each point represents the mean ± S.E.M., and asterisk indicates a significant difference (* $P < 0.05$) between haloperidol plus methamphetamine group (closed triangles, $n = 6$) and haloperidol-treated groups (open triangles, $n = 6$).

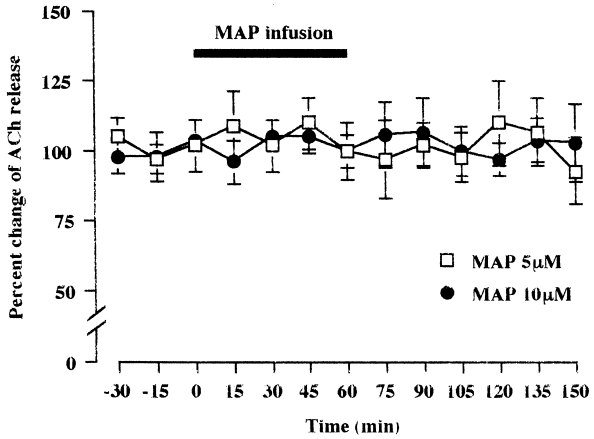

Fig. 3. Effects of methamphetamine infusion on extracellular acetylcholine release in the rat striatum. Basal acetylcholine release was 3.49 ± 0.9 pmol/15 min. Methamphetamine infusion via the dialysis probe did not affect the release of acetylcholine in the rat striatum. Each point represents the mean ± S.E.M. Methamphetamine (open squares, 5 μM, $n = 4$; closed circles, 10 μM, $n = 5$).

at $43.0 \pm 9.0\%$ ($P < 0.01$) at 30 min. A significant increase in acetylcholine release was observed 15 to 60 min after methamphetamine injection. Recovery was observed 75 min later. Haloperidol (0.5 mg/kg, i.p.), a dopamine receptor antagonist, administered intraperitoneally 30 min before the administration of methamphetamine, attenuated the methamphetamine-induced increase ($24.6 \pm 6.8\%$; $P < 0.05$) of acetylcholine release at 30 min (Fig. 2B). Fig. 3 shows that intrastriatal infusion of methamphetamine (5 and 10 μM) had no effect on the release of striatal acetylcholine.

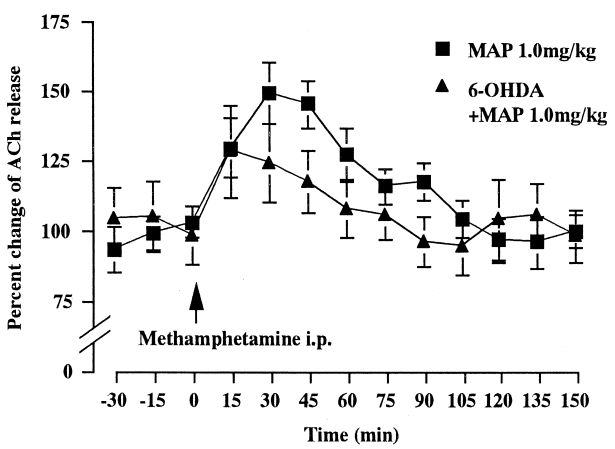

Fig. 4. Effects of methamphetamine on extracellular acetylcholine release following pretreatment with 6-hydroxydopamine (6 μg/3 μl, 7 days before) in the rat striatum. Basal acetylcholine release after pretreatment with 6-hydroxydopamine was 3.81 ± 0.8 pmol/15 min. Pretreatments attenuated the methamphetamine (1.0 mg/kg, i.p.)-induced increase of acetylcholine release. Each point represents the mean ± S.E.M. Methamphetamine (closed squares, $n = 5$); 6-hydroxydopamine (closed triangles, $n = 6$).

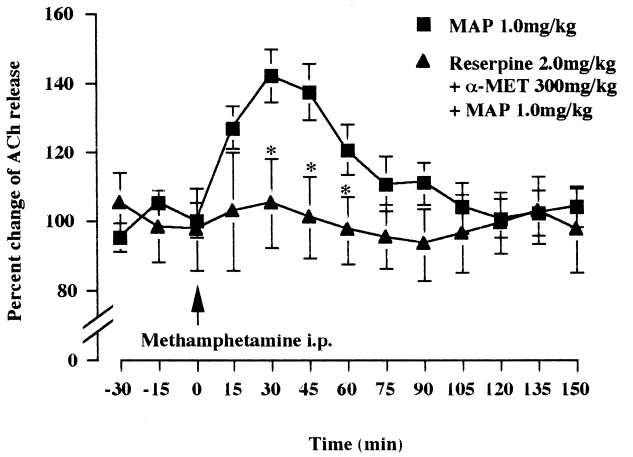

Fig. 5. Effects of methamphetamine on extracellular acetylcholine release following pretreatment with reserpine (2.0 mg/kg, i.p.; 24 h before) plus α-methyl-*p*-tyrosine (300 mg/kg, i.p; 2.5 h before) in the rat striatum. Basal acetylcholine release after pretreatment with reserpine plus α-methyl-*p*-tyrosine was 2.81 ± 0.9 pmol/15 min. Pretreatment reduced the methamphetamine (1.0 mg/kg, i.p.)-induced increase of acetylcholine release. Each point represents the mean ± S.E.M., and asterisks indicate a significant difference ($* P < 0.05$) between reserpine plus α-methyl-*p*-tyrosine group (closed triangles, $n = 6$) and methamphetamine-treated groups (closed squares, $n = 6$).

3.3. Effects of methamphetamine on acetylcholine release following pretreatment with 6-hydroxydopamine or reserpine and α-methyl-p-tyrosine

The striatum dialysates collected from untreated rats contained mean quantities of 0.16 ± 0.05 pmol/40 μl of dopamine, 40.8 ± 4.1 pmol/40 μl of 3,4-dihydroxyphenyl acetic acid and 22.1 ± 3.2 pmol/40 μl of homovanillic acid. In rats pretreated with 6-hydroxydopamine (6 μg/3 μl, 7 days before) or with reserpine (2.0 mg/kg, i.p.; 24 h before) plus α-methyl-*p*-tyrosine (300 mg/kg, i.p.; 2.5 h before), 3,4-dihydroxyphenyl acetic acid and homovanillic acid levels were more than 80% lower than those in untreated rats. Unilateral injection of 6-hydroxydopamine resulted in an acetylcholine release of 3.8 ± 0.8 pmol/15 min after 7 days. Pretreatment with reserpine plus α-methyl-*p*-tyrosine resulted in a basal acetylcholine release of 2.8 ± 0.9 pmol/15 min in the striatum. Microinjection of 6-hydroxydopamine into the substantia nigra attenuated the methamphetamine (1.0 mg/kg)-induced increase ($17.2 \pm 11.0\%$) of acetylcholine release at 45 min (Fig. 4). However, at 15 min, 6-hydroxydopamine treatment showed no effect (Fig. 4). In addition, pretreatment with reserpine plus α-methyl-*p*-tyrosine completely attenuated the increase of acetylcholine release ($5.7 \pm 4.5\%$) induced by 1.0 mg/kg methamphetamine (Fig. 5).

4. Discussion

Our in vivo microdialysis findings indicated that intraperitoneal administration of methamphetamine increases

the release of acetylcholine in the rat striatum. Systemic administration of amphetamine had been shown to enhance the release of acetylcholine in the striatum, using in vivo microdialysis in the freely moving rat (Consolo et al., 1987; Florin et al., 1992). Recently, amphetamine was demonstrated to increase the release of acetylcholine in the striatum of the rat (Mandel et al., 1994; Cadoni et al., 1995; Acquas et al., 1997). The results of the present study agree with these previous findings, suggesting that psychomotor stimulants enhance cholinergic activity in the striatum of freely moving rats.

Since striatal acetylcholine release appears to be closely related to the behavioral state of animals (Damsma et al., 1991; Day et al., 1991), the question arises as to whether the effects of methamphetamine on acetylcholine release are due, at least in part, to the increase in locomotor activity. Methamphetamine- and amphetamine-induced behavioral activation is well known to be mediated by dopamine (Yamanaka et al., 1983; Sharp et al., 1987). For example, amphetamine increases both locomotor activity and striatal acetylcholine release (Damsma et al., 1991). In contrast, raclopride, a dopamine D_2 receptor antagonist, increases striatal acetylcholine release but not locomotor activity (Ögren et al., 1986; Damsma et al., 1991). Furthermore, apomorphine, a dopamine D_1/D_2 receptor agonist, induces locomotor activity and oral behaviour but decreases acetylcholine concentrations (Florin et al., 1992). Therefore, a simple relationship between cholinergic activity and locomotor activity is not consistent with previous observations.

The release of acetylcholine in the rat striatum was found to be regulated by dopamine receptor agonists and antagonists, using in vivo microdialysis (Ajima et al., 1990; Damsma et al., 1990; Hagiwara et al., 1993). In the present experiments, systemic administration of methamphetamine caused acetylcholine release in the striatum to increase. The release of acetylcholine produced by methamphetamine was partially antagonized by haloperidol, indicating that the dopamine receptor is partially involved in the effect of methamphetamine on the release of acetylcholine. It is likely that this effect is mediated by the methamphetamine-induced enhancement of striatal dopamine release. Methamphetamine and amphetamine increase the levels of dopamine in the striatum (Zetterström et al., 1983; Butcher et al., 1988; DeBoer et al., 1992; O'Dell et al., 1993). In the present experiments, apomorphine, a direct dopamine receptor agonist, produced a significant decrease in striatal acetylcholine release. Systemic administration of the dopamine D_2 receptor agonist decreased the release of acetylcholine, whereas the dopamine D_1 receptor agonist significantly increased acetylcholine release in striatum in the absence of an acetylcholinesterase inhibitor (DeBoer and Abercrombie, 1996). In addition, it was 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). These results suggest that dopamine D_1 and dopamine D_2 receptors appear to exert contradictory effects on striatal acetylcholine release. Systemic administration of dopamine D_1 receptor antagonists attenuates the amphetamine-induced increases in striatal acetylcholine release (Imperato et al., 1993; DeBoer and Abercrombie, 1996). Recently, Acquas et al. (1997) demonstrated that striatal infusion of the dopamine D_1 receptor agonists and antagonists did not affect acetylcholine release, and that the dopamine D_1 receptors are not located in the striatum. Together, these results suggest that the indirect dopamine receptor agonist, methamphetamine, increases acetylcholine release in the striatum via a dopamine D_1 receptor of extra-striatal origin.

However, methamphetamine may act more directly on acetylcholine release through cholinergic interneurons in the striatum. In our experiments, intrastriatal administration of methamphetamine did not affect the release of striatal acetylcholine. Similarly, amphetamine administration via a dialysis probe did not affect the release of acetylcholine in the striatum (Mandel et al., 1994). However, local infusion of amphetamine decreases the extracellular striatal acetylcholine concentration in a dose-dependent manner (DeBoer et al., 1992). Thus, psychomotor stimulants such as amphetamine or methamphetamine may not directly cause an increase in striatal acetylcholine release.

Intrastriatal application of methamphetamine (5 and 10 μM) did not influence the release of acetylcholine at a 3.4 mmol/l Ca^{2+} concentration of Ringer's solution (neostigmine 10 μM). In addition, microinfusion of amphetamine (10 μM) decreased the release of acetylcholine when the perfusion solution contained 1.2 mmol/l Ca^{2+}, whereas no effect could be detected at 3.4 mmol/l Ca^{2+} (neostigmine 0.1 μM) (DeBoer et al., 1990; DeBoer et al., 1992). In contrast, amphetamine (10 μM) given via a dialysis probe did not affect the release of striatal acetylcholine at 1.2 mmol/l Ca^{2+} concentration in the perfusion solution (neostigmine 10 μM) in anesthetized rats (Mandel et al., 1994). Although the reasons for this discrepancy are not clear, possible causes may be related to the anesthetic used or to concentration of Ca^{2+} and of the cholinesterase inhibitor. The use of acetylcholinesterase inhibitors may have a significant effect on striatal acetylcholine release. Therefore, the presence of an acetylcholinesterase inhibitor alone may account for this discrepancy, because systemic administration of amphetamine decreases the release of acetylcholine in the striatum in the absence of a cholinesterase inhibitor (DeBoer and Abercrombie, 1996). Recently, systemic administration of amphetamine in a neostigmine (0.1 μM)-containing Ringer's solution was found to increase acetylcholine release (Acquas and Fibiger, 1998). In contrast, at a low neostigmine concentration (0.01 μM), amphetamine significantly decreased the release of acetylcholine in the striatum (Acquas and Fibiger, 1998). Thus, striatal acetylcholine release evaluated with

an in vivo microdialysis method may be due to a complex relationship between Ca^{2+} and cholinesterase inhibitor. Further work is required to elucidate the role of the cholinergic system in neuronal events in the striatum that are related to Ca^{2+}, cholinesterase inhibitor and acetylcholine release induced by psychomotor stimulants.

To investigate whether the methamphetamine-induced increase in acetylcholine release is dependent on the nigrastriatal dopaminergic system, we lesioned striatal dopaminergic neurones by microinjection of 6-hydroxydopamine in the substantia nigra. Although methamphetamine induced a significant increase in the striatal acetylcholine release of normal rats, the striatal acetylcholine release was partially attenuated in 6-hydroxydopamine-pretreated rats. These results are similar to those for rats subjected to pretreatment with haloperidol. In addition, the existence of 6-hydroxydopamine or 5,7-dihydroxytryptamine lesions of ascending-dopaminergic or -serotonergic neurons did not significantly affect the amphetamine-induced acetylcholine release in the anesthetized rat (Mandel et al., 1994). Thus, it seems unlikely that the methamphetamine-induced increase of acetylcholine release is primarily due to the nigrostriatal dopaminergic system involved in dopamine release.

A combination of reserpine and α-methyl-*p*-tyrosine has been shown to completely inhibit the ability of amphetamine to diminish the depolarization-induced release of [^{3}H]acetylcholine in striatal slices (Cantrill et al., 1983). However, the amphetamine-induced acetylcholine release demonstrated using in vivo microdialysis was not modified by reserpine or α-methyl-*p*-tyrosine pretreatment (Cadoni et al., 1995). The present data indicate that combined pretreatment with reserpine and α-methyl-*p*-tyrosine completely blocks the effect of methamphetamine on the release of acetylcholine from the striatum. The results of the present study are consistent with the hypothesis that the increase of acetylcholine release induced by systemic administration of methamphetamine is due to linking of the catecholaminergic and cholinergic systems. On the other hand, the terminals responsible for acetylcholine release within the striatum may arise from cholinergic interneurons intrinsic to the region or from other nuclei containing cholinergic neurons. In addition, striatal cholinergic neurons receive glutaminergic innervation from the frontal cortex, and dopamine D_1 receptor agonists may indirectly increase striatal acetylcholine release by increasing glutaminergic neurotransmission in the striatum (Kitai et al., 1976; Damsma et al., 1991). Modulation of acetylcholine release is caused by the dopaminergic modulation of the glutaminergic system, which is of extra-striatal origin. The extra-striatal origin of the cholinergic innervation responsible for the enhanced acetylcholine release in the striatum remains unclear.

We conclude that systemic administration of methamphetamine increases acetylcholine release from the striatum in freely moving rats, and that the release of acetylcholine is regulated by synergistic interactions between the dopaminergic and catecholaminergic systems.

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