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REDUCTION OF *IN VIVO* BINDING OF [^{3}H]PAROXETINE IN MOUSE BRAIN BY 3,4-METHYLENEDIOXYMETHAMPHETAMINE

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Summary—The effects of 3,4-methylenedioxymethamphetamine (MDMA) on the *in vivo* binding of [^{3}H]paroxetine, a potent and selective 5-hydroxytryptamine (5-HT; serotonin) uptake inhibitor, in the brain of the mouse were studied. The distribution of radioactivity in the brain of the mouse, after intravenous administration of [^{3}H]paroxetine, was significantly altered by pretreatment with MDMA (15 mg/kg, i.p., 3 hr before). The hypothalamus/cerebellum and cerebral cortex/cerebellum ratios, as a function of time, were significantly decreased after the pretreatment with MDMA, indicating that the *in vivo* binding of [^{3}H]paroxetine to uptake sites for 5-HT in the brain of the mouse was significantly decreased by MDMA. These ratios could reflect those of the total binding, to the non-specific binding and free ligand, since the cerebellum has very low levels of binding for [^{3}H]paroxetine. Furthermore, these ratios decreased after pretreatment with MDMA, in a dose-dependent manner. However, the binding of [^{3}H]paroxetine to membranes from the brain of the mouse *in vitro* was not altered by treatment with MDMA. The discrepancy between the *in vivo* binding and *in vitro* binding of [^{3}H]paroxetine in the brain of the mouse is discussed.

Key words—3,4-methylenedioxymethamphetamine, [^{3}H]paroxetine, *in vivo* binding, 5-hydroxytryptamine uptake sites, mouse brain.

3,4-Methylenedioxymethamphetamine (MDMA; Ecstasy) is a ring-substituted analogue of amphetamine, with unique psychoactive properties (Shulgin, 1986). The drug causes both immediate and prolonged changes in central serotonergic systems; such changes include reductions in the concentration of 5-hydroxytryptamine (5-HT; serotonin) and its major metabolite 5-hydroxyindoleacetic acid (5-HIAA), as well as a decrease in the activity of tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of 5-HT (Schmidt, 1987; Schmidt and Taylor, 1987; Stone, Hanson and Gibb, 1987a; Stone, Merchant, Hanson and Gibb, 1987b; Battaglia, Yeh, O'hearn, Molliver, Kuhar and De Souza, 1987; Battaglia, Yeh and De Souza, 1988; Logan, Laverty, Sanderson and Yee, 1988; Schmidt and Taylor, 1988; Peroutka, 1988). Furthermore, it has been reported that the density of uptake sites for 5-HT, labelled by [^{3}H]paroxetine *in vitro*, in the brain of the rat was significantly decreased by the administration of MDMA (Battaglia *et al.*, 1987; Battaglia *et al.*, 1988; Peroutka, 1988).

However, it has been reported that the density of uptake sites for 5-HT was decreased in the brain tissue of depressed patients (Perry, Marshall, Blessed, Tomlinson and Perry, 1983), in the frontal cortex of suicide victims (Stanley, Virgilio and Gershon, 1982), in the brains of patients with Alzheimer's disease (D'Amato, Zweig, Whitehouse, Wenk, Singer, Mayeux, Price and Snyder, 1987b; Marcusson, Alafuzoff, Backstrom, Ericson, Gottfries and Winblad, 1987) and in the brains of patients with Parkinson's disease (D'Amato *et al.*, 1987b; Raisman, Cash and Agid, 1986). The development of positron emission tomography (PET) made it possible to study *in vivo* the neuronal receptors in the intact human brain. The *in vivo* study of uptake sites for 5-HT in the human brain, using PET would be, therefore, of great interest due to their possible biological role in relation to these diseases and to the pharmacological study of various drugs. More recently, it has been demonstrated that [^{3}H]paroxetine would be a suitable radioligand for the *in vivo* labelling of uptake sites for 5-HT in the brain of the mouse (Hashimoto and Goromaru, 1988; Hashimoto and Goromaru, unpublished; Scheffel and Hartig, 1989). The present study was undertaken to examine the neuropharmacological effects of MDMA on the uptake sites for 5-HT in the brain of the mouse using the *in vivo* binding of [^{3}H]paroxetine.

METHODS

Animals

Male ddy mice, weighing 30–35 g, were used. The animals were housed in a group of 10 animals in a

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cage. They were maintained under standard conditions (light on from 6:00 to 18:00 hr, room temperature 23 ± 1°C, humidity 55 ± 5%) with free access to food and water.

Materials

[^{3}H]Paroxetine [26.5 Ci/mmol (980.5 GBq/mmol) and 29.4 Ci/mmol (1087.8 GBq/mmol)] was purchased from New England Nuclear (Boston, Massachussetts, U.S.A.). The [^{3}H]MDMA [85.1 Ci/mmol (3.15 TBq/mmol)] was synthesized by *N*-methylation of 3,4-methylenedioxyamphetamine (MDA), as described previously (Hashimoto, Hirai and Goromaru, 1990). Paroxetine hydrochloride was donated from Beecham Pharmaceuticals (Surrey, U.K.). Both MDMA and MDA were synthesized from 3,4-methylenedioxyphenyl-2-propanone (Fluka AG, Switzerland) and methylamine or ammonium acetate, as described previously (Braun, Shulgin and Braun, 1980). Other chemicals were purchased commercially.

In vivo binding of [^{3}H]paroxetine

Mice were injected intravenously with 0.2 ml [about 2.7 μCi (100 kBq)] of [^{3}H]paroxetine. The mice were lightly anaesthetized with ether and killed by decapitation at various times after the injection of the radiotracer. Blood, hypothalamus, cerebral cortex and cerebellum were quickly removed and weighed, each sample being incinerated by a automated combustion system (Aloka, ASC-113) and the radioactivity in each sample was determined by a liquid scintillation counter (Aloka, LSC-1000). Radioactivity was expressed as the percentage of the dose injected, per gram tissue (% dose/g). In order to examine the effects of MDMA on the *in vivo* binding of [^{3}H]paroxetine in the brain of the mouse, MDMA was injected intraperitoneally into mice, 3 h before the injection of the radioligand.

In vitro binding of [^{3}H]paroxetine

Brains (minus cerebellum and pons-medulla) from individual vehicle- or MDMA (15 mg/kg, i.p., 3 hr before)-pretreated mice were removed. The brain tissue was homogenized in 50 volumes of ice-cold buffer (50 mM Tris–HCl, 120 mM NaCl, 5 mM KCl, pH 7.4 at 25°C), using a Kinematica Polytron homogenizer (Luzern, Switzerland), at a setting 5 for 30 sec. The homogenate was centrifuged at 48,000 *g* for 10 min. The resulting pellet was resuspended in 50 volumes of ice-cold buffer and recentrifuged. The final pellet was resuspended in the same buffer to a concentration of 1–1.5 mg protein/ml, as measured using the method of Lowry *et al.* (Lowry, Rosebrough, Farr and Randall, 1951).

The binding of [^{3}H]paroxetine was carried out with a slight modification of the original protocol (Habert, Graham, Tahraoui, Claustre and Langer, 1985). Aliquots (200 μg protein) of membrane suspension were incubated with [^{3}H]paroxetine (30–2000 pM) at 37°C in a final volume of 1 ml for 60 min. After the addition of 4 ml of ice-cold buffer, the homogenates were rapidly filtered through Whatman GF/C filters, using a 24-channel cell harvester (Brandel, Gaithersburg, Maryland, U.S.A.). Filters were routinely pretreated with 0.05% polyethyleneimine before use. Finally, the filters were washed with three 5 ml rinses of ice-cold buffer. The radioactivity trapped by the filters was determined by a liquid scintillation counter. Non-specific binding was estimated in the presence of 1 μM paroxetine.

The data from equilibrium saturation were analyzed by means of the least squares linear regression method, using a Damping Gauss–Newton algorithm.

The inhibition experiment was analyzed by conventional graphical techniques by means of the iterative non-linear least squares method, using a Damping Gauss–Newton algorithm. The IC_{50} value for the drug was defined as the concentration that resulted in a 50% inhibition of specific binding. The K_i values was calculated using the formula $K_i = IC_{50}/(1 + C/K_d)$ (Cheng and Prusoff, 1973), where C is the concentration of [^{3}H]paroxetine employed and K_d the equilibrium dissociation constant.

Stability of [^{3}H]paroxetine in the brain of the mouse

About 10.8 μCi (400 kBq) of [^{3}H]paroxetine was injected intravenously into the vehicle- or MDMA (15 mg/kg, i.p., 3 hr before)-treated mice. Three hr after the injection of the radiotracer, the mouse was lightly anaesthetized with ether and killed by decapitation and the brains were quickly removed. The brain was homogenized with 1.0 ml of phosphate buffer (0.2 N, pH 7.4) and 0.5 ml of ethanol, containing, 1 mg of paroxetine, was added to 0.5 ml of brain homogenate, then the radioactive materials were extracted. The extractable solution was concentrated by a rotary evaporator and its was analyzed by high performance liquid chromatography [HPLC: Column; Shim-pack CLC-ODS (5 μm, 6.0 mm i.d. × 15 cm), mobile phase; acetonitrile: 1% aqueous triethylamine acetate (pH 4.0) = 4: 6, flow rate; 2 ml/min, detector; UV (254 nm)], as described previously (Hashimoto and Goromaru, 1989). The radioactivity in each fraction was determined by a liquid scintillation counter.

Measurement of the content of 5-HT and 5-HIAA in the brain of the mouse

Tissue levels of 5-HT and 5-HIAA were measured by HPLC with electrochemical detection. The tissues were weighed and homogenized with 0.1 N $HClO_4$ containing 0.1% cystein. *N*-Acetyl 5-HT (100 ng/ml) was added as an internal standard to allow recoveries to be determined. After centrifugation at 4000 *g* for 15 min (4°C), the fractions of supernatant were filtered through a 0.2 μm microfilter system (Millipore Ltd, Tokyo, Japan) and 20 μl were injected onto a reverse-phase column [TSKgel ODS-80T_M (5 μm, 4.6 mm i.d. × 25 cm)] and eluted with a

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mobile phase [monochloroacetic acid (0.15 M), disodium ethylene diamine tetra acetic acid (EDTA) (0.2 mM), 1-octanesulfonic acid (0.1 mM) in 15% methanol at pH 2.9], at a flow rate of 0.8 ml/min. The detector potential was set at +0.80 V. The 5-HT and 5-HIAA were quantified by comparison with standards of known concentration.

Distribution and in vivo stability of [^{3}H]MDMA in the brain of the mouse

Mice were injected intraperitoneally with 0.2 ml (about 1 μCi (37 kBq) of [^{3}H]MDMA (15 mg/kg). The mice were lightly anaesthetized with ether and killed by decapitation 3 hr after injection of [^{3}H]MDMA. The distribution of radioactivity in blood and brain was determined as described above.

To examine the *in vivo* stability of [^{3}H]MDMA in the brain of the mouse, [^{3}H]MDMA [15 mg/kg, 10 μCi (370 kBq)] was injected intraperitoneally into the mouse. The mouse was killed by decapitation 3 hr after the intraperitoneal injection of [^{3}H]MDMA and the brain was quickly removed. The brain as homogenized with 1.0 ml of phosphate buffer (0.2 N, pH 7.4) and 0.5 ml of ethanol was added to 0.5 ml of brain homogenate, then the radioactive materials were extracted. The extractable solution as analyzed by thin layer chromatography (TLC: silicagel; $CHCl_3$:MeOH:NH_4OH = 9:1:0.1, *Rf* value = 0.35). The radioactivity in each fraction was determined by a liquid scintillation counter.

Statistics

The statistical evaluation of the multigroup data was performed by a one-way analysis of variance (ANOVA), followed by the Scheffe's test for multiple comparisons. The statistical analysis of two-sample data was performed by Student's *t*-test. The criterion for significance was $P < 0.05$.

RESULTS

Figure 1 shows the time course of radioactivity in the blood, hypothalamus, cerebral cortex and cerebellum after the intravenous administration of [^{3}H]paroxetine. The time course of radioactivity in the mice, after injection of [^{3}H]paroxetine, was significantly altered by pretreatment with MDMA (15 mg/kg, i.p., 3 hr before), as shown Fig. 1(B). Furthermore, the half-life of radioactivity in the blood and brain after intravenous injection of [^{3}H]paroxetine was increased by pretreatment with MDMA. The ratios of hypothalamus/cerebellum and cerebral cortex/cerebellum, as a function of time, were significantly decreased by pretreatment with MDMA, as shown in Fig. 2. Moreover, the distribution of radioactivity in the blood and brain, 3 hr after the injection of [^{3}H]paroxetine, was increased by pretreatment with MDMA (0, 1, 5, 10 and 15 mg/kg, i.p., 3 hr before) in a dose-dependent manner (Fig. 3A). However, the ratios of hypothalamus/cerebellum and cerebral cortex/cerebellum were decreased by pretreatment with MDMA, in a dose-dependent manner (Fig. 3B).

The radioactivity in brain after administration of [^{3}H]paroxetine in the vehicle- and MDMA (15 mg/kg, i.p., 3 hr before)-treated mice, was found to be due to unmetabolized [^{3}H]paroxetine. This was found by HPLC analysis (Fig. 4).

Table 1 shows the effects of MDMA on the concentrations of 5-HT and 5-HIAA in the brain of

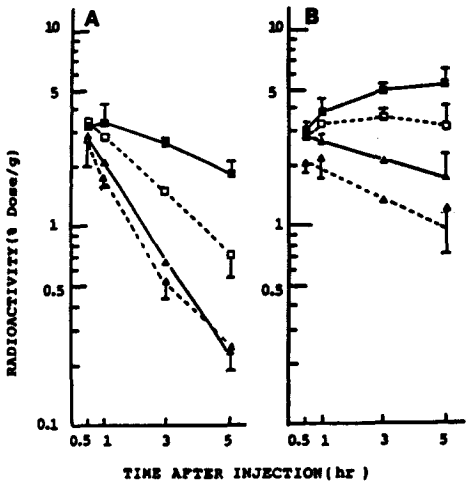

Fig. 1. The distributions of radioactivity in mice pretreated with (A) vehicle and (B) MDMA (15 mg/kg, i.p., 3 hr before), after intravenous administration of [^{3}H]paroxetine. Radioactivity in the blood (△), hypothalamus (■), cerebral cortex (□) and cerebellum (▲) was expressed as the percentage of the injected dose, per gram tissue (% dose/g). Values are presented as an average ± SD of 3 mice for each point.

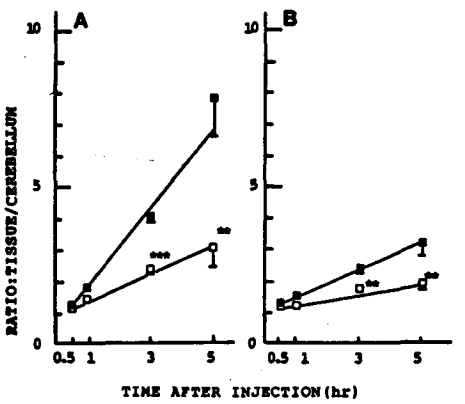

Fig. 2. Effect of MDMA on (A) hypothalmus/cerebellum and (B) cerebral cortex/cerebellum ratios, as a function of time. The data in the vehicle group (■) and in the MDMA-pretreated group (□) was from Figure 1. Values are presented as an average ± SD of 3 mice for each point. Asterisks indicate that the value in MDMA-pretreated mice was significantly different from the value in control mice, at corresponding times (**$P < 0.01$; ***$P < 0.001$ using Scheffe's test).

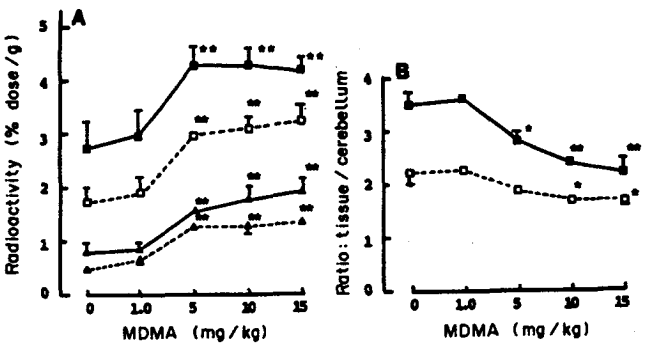

Fig. 3. Dose-effects of MDMA on the *in vivo* binding of [^{3}H]paroxetine in the brain of the mouse. The mice were injected intravenously with [^{3}H]paroxetine, 3 hr after the administration of various doses of MDMA (0, 1.0, 5.0, 10 and 15 mg/kg, i.p., expressed as the free base). Three hr after the injection of the radiotracer, the distribution of radioactivity in the mice was determined. (A) Radioactivity in the blood (△), hypothalamus (■), cerebral cortex (□) and cerebellum (▲), was expressed as the percentage per gram tissue (% dose/g). Values are presented as an average ± SD of 3 mice for each point. (B) The values of the hypothalamus/cerebellum (■) and cerebral cortex/cerebellum (□) ratios were data from Figure 3(A). Values are presented as an average ± SD of 3 mice for each point. Asterisks indicate that the value of MDMA-pretreated mice was significantly different from the value in control mice ($^*P < 0.05$; $^{**}P < 0.01$ using Scheffe's test).

the mouse. The content of 5-HT in the hypothalamus and cerebral cortex was not altered by administration of MDMA (15 mg/kg, i.p., 3 hr before), whereas the content of 5-HIAA in the brain of the mouse was significantly decreased by MDMA.

Treatment with MDMA (15 mg/kg, i.p., 3 hr before) did not affect the maximum number of binding sites (B_{max}) or the apparent equilibrium dissociation constant (K_d) of the binding sites, labelled with [^{3}H]paroxetine, as shown in Table 2.

The distribution of radioactivity in the blood and brain of the mouse, 3 hr after the intraperitoneal injection of [^{3}H]MDMA (15 mg/kg) were 0.537 and 0.583 (% dose/g tissue), respectively (Table 3). As shown in Figure 5, it was found by TLC analysis that radioactivity in the brain of the mouse, 3 hr after the intraperitoneal injection of [^{3}H]MDMA (15 mg/kg), was due to unmetabolized [^{3}H]MDMA.

Inhibition constants (K_i values) for MDMA and MDA on the binding of [^{3}H]paroxetine to membranes from the brain of the mouse *in vitro* at 37°C were 4.86 and 6.18 μM, respectively (Table 4). Furthermore, the inhibition of binding of [^{3}H]paroxetine by MDMA and MDA appeared to be monophasic and gave a pseudo-Hill coefficient close to unity (Table 4).

DISCUSSION

The present results show that the time course of radioactivity in the blood and brain after intravenous administration of [^{3}H]paroxetine was dynamically altered by pretreatment with MDMA (15 mg/kg). Although the mechanisms underlying the MDMA-induced increased in the half-life of radioactivity in the blood and brain are currently unknown, they might be caused by the alteration of some

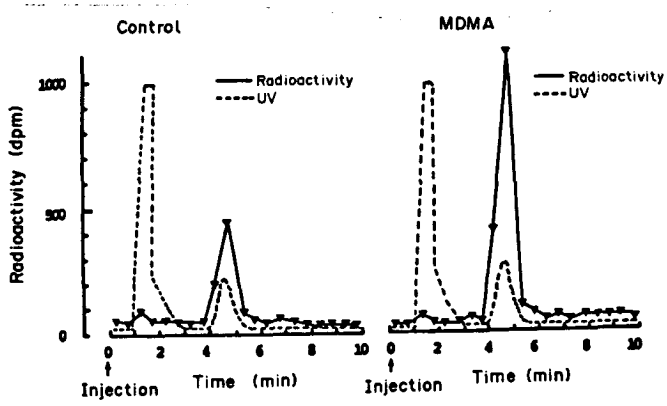

Fig. 4. The HPLC analysis of radioactive materials in the brain of the mouse at 3 hr after the intravenous administration of [^{3}H]paroxetine. Column; Shim-pack CLC-ODS, Mobile phase; acetonitrile: 1% aqueous triethylamine acetate (pH 4) = 4:6, Flow rate; 2 ml/min, Detector; UV (254 nm), Retention time of paroxetine (4.6 min).

Table 1. Concentrations of 5-HT and 5-HIAA in the brain of the mouse

	Tissue (ng/mg)	
	5-HT	5-HIAA
Hypothalamus		
Control	0.880 ± 0.083	1.200 ± 0.303
MDMA	0.890 ± 0.168	0.596 ± 0.056**
Cerebral cortex		
Control	0.394 ± 0.079	0.289 ± 0.046
MDMA	0.396 ± 0.148	0.130 ± 0.029**

Each value represents the mean ± SD of four mice.
**$P < 0.01$ when compared with Control group (Student's t-test).

physiological functions, such as the renal clearance rate or metabolic rate of [^{3}H]paroxetine. The radioactivity in the blood, after the injection of [^{3}H]paroxetine, was increased by pretreatment with MDMA, resulting in greater radioactivity in brain. Thus, the increase of the radioactivity in the cerebellum produced by MDMA might be due to an increase in the amount of non-specific binding, plus free ligand in the brain. Furthermore, the hypothalamus/cerebellum and cerebral cortex/cerebellum ratios, as a function of time, were significantly decreased by pretreatment with MDMA (15 mg/kg), indicating that *in vivo*, the binding of [^{3}H]paroxetine to uptake sites for 5-HT in the brain, was reduced by MDMA. These ratios could reflect those of the total binding to the non-specific binding and the free ligand, since the cerebellum has very low levels of uptake sites for 5-HT (Kuhar, Aghajanian and Roth, 1972; D'Amato, Largent, Snowman and Snyder, 1987a; De Souza and Kuyatt, 1987). Also, it was shown that the hypothalamus/cerebellum and cerebral cortex/cerebellum ratios were decreased by pretreatment with MDMA, in a dose-dependent manner. Furtheremore, the *in vivo* stability in the brain at 3 hr after the intravenous injection of [^{3}H]paroxetine, was not altered by pretreatment with MDMA, indicating that the MDMA-induced alteration in the radioactivity in brain might be due to alteration in the binding of [^{3}H]paroxetine itself, and not to the metabolites of [^{3}H]paroxetine.

Marked species differences are found in the degree and duration of the central serotonergic effects of MDMA (Stone *et al.*, 1987b; Logan *et al.*, 1988; Peroutka, 1988). It has been found that MDMA appeared to be much less potent in its ability to affect central 5-HT pathways in mice (Stone *et al.*, 1987b; Battaglia *et al.*, 1988; Logan *et al.*, 1988; Peroutka, 1988), whereas MDMA has been implicated as a potent serotonergic neurotoxin in rats (Schmidt, 1987; Schmidt and Taylor, 1987; Stone *et al.*, 1987a; Stone *et al.*, 1987b; Battaglia *et al.*, 1987; Battaglia *et al.*, 1988; Logan *et al.*, 1988; Peroutka, 1988). The present results show that the content of 5-HT in the hypothalamus and cerebral cortex, 3 hr after an injection of MDMA, was not altered, when compared with the control. Also, the binding of [^{3}H]paroxetine to membranes from the brain of the mouse, *in vitro* was not altered by treatment with MDMA, indicating that [^{3}H]paroxetine-labelled uptake sites for 5-HT in the brain of the mouse were not destroyed by treatment with MDMA. Peroutka (1988) reported that no effect on [^{3}H]paroxetine-labelled uptake sites for 5-HT could be detected in mice after a single 30 mg/kg injection of MDMA. Battaglia *et al.* (1988) also reported that the density of uptake sites for 5-HT, labelled by [^{3}H]paroxetine in the brain of the mouse was not altered by repeated systemic administration of MDMA. Taken together, it was found that mice

Table 3. Distribution of radioactivity in mice 3 hr after the intraperitoneal administration of [^{3}H]MDMA (15 mg/kg)

	% Dose/g tissue
Blood	0.537 ± 0.04
Brain	0.583 ± 0.05

Each value is the mean ± SD of 3 mice.

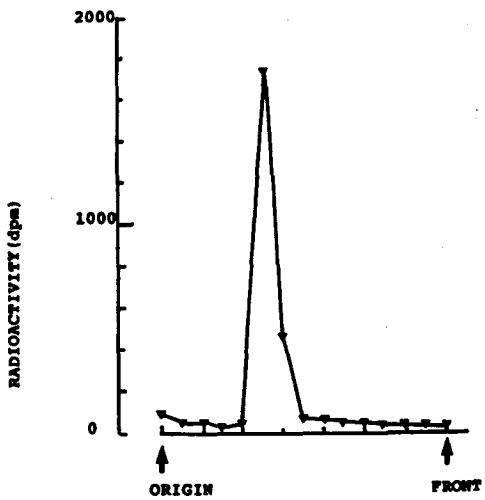

Fig. 5. The TLC analysis of radioactive materials in the brain of the mouse 3 hr after the intraperitoneal administration of [^{3}H]MDMA (15 mg/kg). Solvent system; $CHCl_3$:MeOH:NH_4OH = 9:1:0.1, *Rf* value of MDMA (0.35).

Table 2. *In vitro* binding data for [^{3}H]paroxetine

	K_d (pM)	B_{max} (fmol/mg protein)	N
Control	78.6 ± 6.75	565.0 ± 24.3	6
MDMA	77.7 ± 7.35	562.6 ± 29.9	9

Equilibrium saturation isotherms of [^{3}H]paroxetine (30–2000 pM) to membranes from the brain of the mouse were determined at 37°C, as described in the text.
The K_d and B_{max} values are presented as the mean ± SD of n experiments.

Table 4. Inhibition by MDMA and MDA of the binding of [^{3}H]paroxetine to membranes of the brain of the mouse at 37°C

	K_i (μM)	nH
MDMA	4.86 ± 0.05	0.922 ± 0.02
MDA	6.18 ± 2.55	0.901 ± 0.02

Each value presents the mean ± SD of 3 determinations done in duplicate.

were relatively insensitive to the neurotoxic effects of MDMA.

More recently, it has been reported that, after the administration of MDMA in mice, MDA was identified as a metabolite of MDMA (Fitzgerald, Blanke, Rosecrans and Glennon, 1989), indicating that the *N*-methyl group of MDMA is cleaved off in the periphery. Therefore, the distribution of MDMA in the brain of the mouse was studied after administration of [^{3}H]MDMA (15 mg/kg). A relatively large amount of MDMA was found in the brain 3 hr after the injection of [^{3}H]MDMA (15 mg/kg). This was known, since the radioactivity in the brain was due to unmetabolized [^{3}H]MDMA, as was discovered by TLC analysis. Since MDA is formed by *N*-demethylation of MDMA in the periphery (Fitzgerald *et al.*, 1989), nonradioactive MDA and radioactive metabolites may exist in the blood and other peripheral organs. Thus, MDA formed by *N*-demethyletion of MDMA in the periphery would be able to enter rapidly into the brain. The TLC analysis indicated that the radioactive metabolites were not detected in the brain 3 hr after the administration of [^{3}H]MDMA (15 mg/kg). From the inhibition experiment of the binding of [^{3}H]paroxetine *in vitro*, it was found that MDMA and MDA potently inhibited the binding of [^{3}H]paroxetine to membranes from the brain of the mouse at 37°C. Taken together, the results suggest that the reduction of the *in vivo* binding of [^{3}H]paroxetine to uptake sites for 5-HT in the brain of the mouse by MDMA might be, in part, due to inhibition caused by MDMA and its metabolite MDA in the brain, and not to the destruction of uptake sites for 5-HT by MDMA. Moreover, a mechanism that rapidly alters the binding of [^{3}H]paroxetine *in vivo*, but not *in vitro*, might exist in brain.

In conclusion, the present results show that *in vivo* binding of [^{3}H]paroxetine in the brain of the mouse was significantly altered by pretreatment with MDMA. The hypothalamus/cerebellum and cerebral cortex/cerebellum ratios, as a function of time, were significantly decreased by pretreatment with MDMA, indicating that the *in vivo* binding of [^{3}H]paroxetine to uptake sites for 5-HT in the brain of the mouse was reduced by pretreatment with MDMA. The present results suggest that the reduction of *in vivo* binding of [^{3}H]paroxetine by treatment with MDMA might be, in part, due to inhibition caused by MDMA and its metabolite MDA, which exist in the brain and not to the degeneration of 5-HT nerve terminals produced by MDMA. Furthermore, it would be possible to study *in vivo*, the drug interactions, related to the uptake sites for 5-HT in intact human brain, using [^{18}F]paroxetine and PET, if high specific activity [^{18}F]paroxetine, labelled with positron emitter (^{18}F; half-life: 110 min), could be prepared.

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