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Repeated Clorgyline Treatment Inhibits Methamphetamine-induced Behavioral Sensitization in Mice

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Following the expression of the behavioral sensitization by repeated administration of methamphetamine (METH) (1 mg/kg, intraperitoneal (i.p.), once per day for five consecutive days), male ICR mice were treated with clorgyline (1 mg/kg, subcutaneous, once per day for five consecutive days), a monoamine oxidase-A inhibitor. Two hours after the final treatment with clorgyline, the mice were challenged with METH (1 mg/kg, i.p.) and locomotor activity was measured for 1 h. The mice treated with clorgyline showed a significant decrease in both vertical locomotion and horizontal rearing, compared with those treated with saline. Clorgyline treatment altered the effect of single METH challenges on apparent dopamine turnover in the cerebral cortex of the mice sensitized to METH. These results suggested a possible association of the inhibition by clorgyline of METH-induced behavioral sensitization with the alteration of dopamine turnover in the cerebral cortex of the mouse.

KEY WORDS: Behavioral sensitization; cerebral cortex; clorgyline; dopamine; methamphetamine; monoamine turnover.

INTRODUCTION

Repeated administration of methamphetamine (METH) induces a progressive augmentation of locomotor activity in response to the same drug in rodents (1–6). This phenomenon is called reverse tolerance or behavioral sensitization. The drugs of abuse that induce behavioral sensitization enhance dopaminergic transmission in the brain, which results in hyperlocomotion and reinforcing effects (6,7).

In the brains of mammals, there are two metabolic pathways for dopamine inactivation, that is, monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) pathways. Dopamine in the mouse brain under normal physiological conditions is largely metabolized by MAO-A, one of the two isozymes of MAO (8). Dopamine is also one of the physiological substrates for COMT (9). These two pathways effectively compensated each other on the knockout of the genes for MAO-A and MAO-B (8) and the COMT gene (10), suggesting the physiological importance of the two dopamine-metabolic pathways.

In mice, hyperlocomotion induced by a single administration of METH was significantly blocked by pretreatment with clorgyline, known as a MAO-A inhibitor (11), via an alteration of apparent 5-hydroxytryptamine (serotonin, 5-HT) turnover in the region of the striatum and accumbens (12). The present study was undertaken to investigate whether or not clorgyline inhibits METH-induced behavioral sensitization in mice. There are several reports showing the blockade of METH-induced behavioral sensitization by chemicals such as gabapentin and nitric oxide synthase inhibitors (13,14). In order to

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effectively block behavioral sensitization, these chemicals needed to be administered prior to repeated treatment with METH. In contrast, our results indicated that clorgyline treatment effectively blocked behavioral sensitization when administered after repeated METH administration.

EXPERIMENTAL PROCEDURE

Animals

Male ICR mice (5-week-old at purchase; Japan SLC, Shizuoka, Japan) were housed in groups of 3–6 in a temperature—(22 ± 2 °C) and humidity—(50 ± 10%) controlled environment under a 12-h light/dark cycle (lights on at 07:00 h) with food and water available *ad libitum* except during the locomotor activity measurements using the Supermex apparatus. Animal handling and care were conducted according to the NIH guidelines (15) and all experiments were approved by the Institutional Animal Research Committee. Every effort was made to minimize the number of animals used and their suffering. After at least seven days' habituation in this facility, mice were used in the experiments as follows.

Behavioral Analyses

Mice (n = 48) were weighed (31–37 g on Day 1) and divided into four groups (n = 12 each). As shown in Table I, all mice were injected intraperitoneally (i.p.) with 0.1 ml/10 g of sterile saline on Day 1. This procedure was required to reduce the variance of data on locomotor activity on Day 2 and thereafter (12,16). On Days 2–11, the mice in each group were subjected to the treatment and measurement protocols as shown in Table I and Fig. 1. No significant effect of the acute (e.g., a single administration) or subchronic (e.g., 3 days) treatment of the mice with clorgyline on METH-induced behavioral sensitization was observed in our preliminary examinations (data not shown). Based on the examinations, we chose the treatment protocol as shown Table I. The doses of drugs refer to the weight of salt. All drugs were dissolved in sterile saline. Clorgyline was administered subcutaneously (s.c.) in a volume of 0.05 ml/10 g of body weight. The METH was administered i.p. in a volume of 0.1 ml/10 g of body weight. The same volume of saline was used for the control. The locomotor activity was measured in a transparent acrylic box (37 cm × 24 cm × 27 cm) in a quiet, ventilated chamber (53 cm × 45 cm × 45 cm) equipped with an infrared sensor to detect thermal radiation from the animals (for horizontal locomotion; Supermex; Muromachi Kikai Co., Tokyo, Japan) and a beam sensor (for rearing; 24-cm wide, at a height of 7 cm; Muromachi Kikai Co.) which are linked to a PC computer. Behavioral activation was defined by counting the number of signal changes in sensor elements from infrared pyroelectric sensors, which detect the body heat of an animal (horizontal locomotion) and by counting the number of beam breaks by the animal (vertical rearing) recorded during each 1-h testing session (Fig. 1). During the measurements, mice were fed tap water *ad libitum*. After the measurements on Days 2–10, mice were returned to their home cages. All experiments were performed between 9:00 and 16:00. All mice either maintained or gained body weight during the experiments (data not shown). On Day 11, mice were killed by cervical dislocation and decapitation 1 h after the METH challenge (Fig. 1). The brains were immediately removed, and the cerebral cortices, regions of the striata and accumbens, and regions of the thalami and hypothalami were isolated, weighed, and frozen in liquid nitrogen for assays by high-performance liquid chromatography (HPLC).

Table I. Schedule for Drug Administration

Test day	1	2–6	7–10	11
Group				
1	S	S	S	S/M
2	S	S	C	C/M
3	S	M	S	S/M
4	S	M	C	C/M

Note: Mice of all four groups (n = 12 each) received 0.1 ml/10 g saline injection (i.p.) on test Day 1 and were then subjected to their own group schedule. Drug solutions were prepared daily and administered by i.p. injection in a volume of 0.1 ml/10 g of body weight or s.c. injection in a volume of 0.05 ml/10 g of body weight. S, 0.1 ml/10 g saline injection (i.p.) during test Days 1–6, and 0.05 ml/10 g saline injection (s.c.) during test Days 7–10; M, 1 mg/kg methamphetamine injection (i.p.); C, 1 mg/kg clorgyline injection (s.c.); S/M, 1 mg/kg methamphetamine injection (i.p.) 2 h after 0.05 ml/10 g saline injection (s.c.); C/M, 1 mg/kg methamphetamine injection (i.p.) 2 h after 1 mg/kg clorgyline injection (s.c.).

Measurement of Levels of Monoamines and Their Metabolites

Each frozen brain sample was homogenized with a Teflon/glass homogenizer in 10–20 volumes (w/v) of ice-cold 0.1 N perchloric acid with 30 μM Na_2EDTA containing 3,4-dihydroxybenzylamine hydrobromide and isoproterenol as internal standards for the catechols and for the indoles, respectively. The homogenates were centrifuged at 10,000 × g for 10 min at 4 °C and the supernatants were filtered through a 0.20 μm membrane filter (Millipore Co., Bedford, MA, USA). The filtrates (10 μl) were injected directly into an HPLC system (system controller, model SCL-10A; autoinjector, model SIL-10A; pump, model LC-10AD; Shimadzu Co., Kyoto, Japan) equipped with a reversed-phase ODS-column (MCM column 150; 4.6 × 150 mm; MC Medical, Inc., Osaka, Japan) and an electrochemical detector (Coulochem Model 5100A, ESA Inc., Chelmsford, MA, USA). The column temperature was maintained at 24 °C, and the detector potentials were set at +0.40 V, +0.15 V and −0.35 V on the conditioning cell, and Detectors 1 and 2, respectively. The mobile phase was a 1000 : 35.2 : 85.8 (v/v) mixture of a buffer (50 mM Na_2HPO_4, 50 mM citric acid, 4.4 mM 1-heptanesulfonic acid and 0.1 mM Na_2EDTA, pH 3.0), acetonitrile and methanol, and the flow rate was set at 0.9 ml/min (12).

Reagents

The METH hydrochloride was purchased from Dainippon Pharmaceutical Co. (Osaka, Japan). *N*-Methyl-*N*-propargyl-3-(2,4-dichlorophenoxy) propylamine hydrochloride (clorgyline) and all standard reagents for HPLC were from Sigma–Aldrich (St. Louis, MO, USA). All other chemicals used were of the highest commercially available purity.

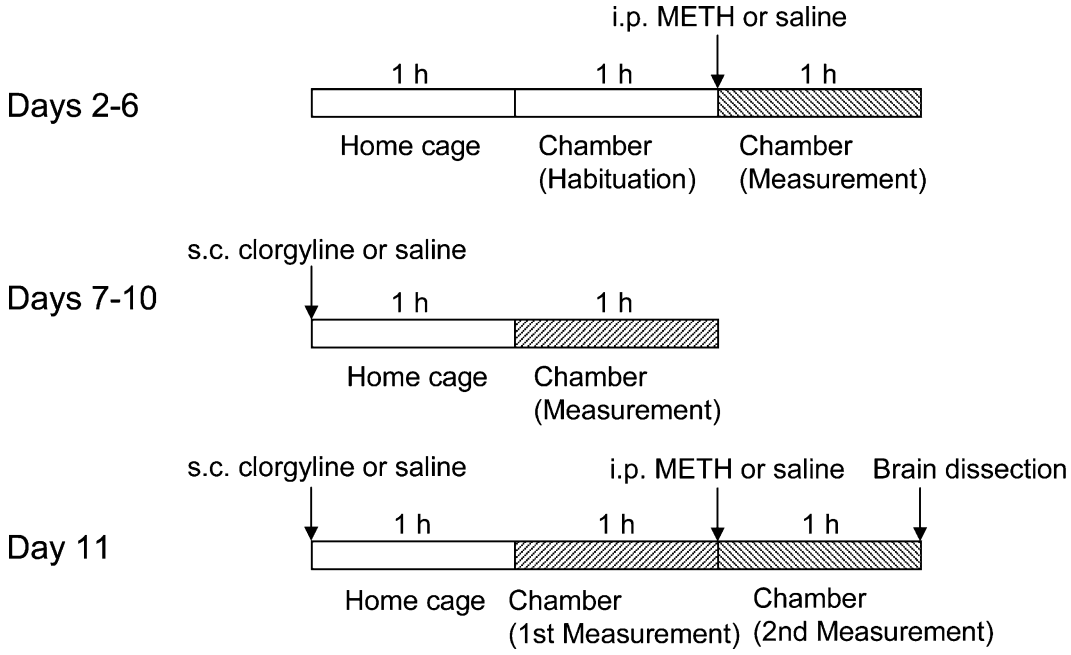

Fig. 1. Schematic representation of the experimental protocol on test Days 2–11. All mice were injected with 0.1 ml/10 g (i.p.) of saline on Day 1 to reduce the variance of data on locomotor activity on Day 2 and the following days. Arrows show the time when mice were injected with drug solutions indicated or the brains were removed and dissected for HPLC analysis. Horizontal locomotion and vertical rearing were measured during the periods indicated by hatched bars. METH = methamphetamine.

Statistical Analysis

Values are shown as means with bars representing the standard errors of the means (S.E.M.). Statistical analysis was performed using a one-way or two-way analysis of variance (ANOVA) using the computer program Statview 5.0 for Apple Macintosh (SAS Institute Inc., Cary, NC, USA). A P value of less than 0.05 was considered a statistically significant difference.

RESULTS

Locomotor Activities

During Days 2–6, repeated administration of METH (1 mg/kg, i.p., once per day for five consecutive days) induced a significant enhancement of locomotion (Fig. 2a) and rearing (Fig. 2b), compared with control mice (Groups 3 and 4 vs. Groups 1 and 2; $F(2,132) = 9.818$, $P < 0.001$ and $F(2,132) = 7.714$, $P < 0.001$ for locomotion and rearing, respectively). During Days 7–11 (first measurement, see Fig. 1), repeated administration of clorgyline (1 mg/kg, s.c., once per day for five consecutive days) had no effect on spontaneous locomotion (Fig. 2a) and rearing (Fig. 2b), compared with control mice (Groups 2 and 4 vs. Groups 1 and 3; $F(2,132) = 0.126$, $P = 0.8821$ and $F(2,132) = 0.068$, $P = 0.8231$ for locomotion and rearing, respectively). On Day 11 (second measurement), a single METH challenge induced significant locomotor activity and rearing in sensitized mice, compared with control animals (Groups 3 and 4 vs. Groups 1 and 2, two-way ANOVA, $F(1,44) = 5.981$, $P < 0.05$ and $F(1,44) = 6.477$, $P < 0.05$ for locomotion and rearing, respectively). Repeated clorgyline treatment significantly suppressed METH-induced hyperactivity (both locomotion and rearing) (Groups 1 and 3 vs. Groups 2 and 4, two-way ANOVA, $F(1,44) = 4.774$, $P < 0.05$ and $F(1,44) = 5.507$, $P < 0.05$ for locomotion and rearing, respectively).

Levels of Monoamines and Their Metabolites

The results obtained from the HPLC-based measurements of the levels of monoamines and their metabolites after the second measurement on Day 11 are presented in Table II. The tissue content of dopamine did not change in any region of the brain tested. As for dopamine metabolites, repeated treatment with clorgyline significantly decreased the tissue contents of 3,4-dihydroxyphenylacetic acid (DOPAC) in the cerebral cortex and the striatum and accumbens ($F(1,44) = 77.432$, $P < 0.001$ and $F(1,44) = 34.403$,

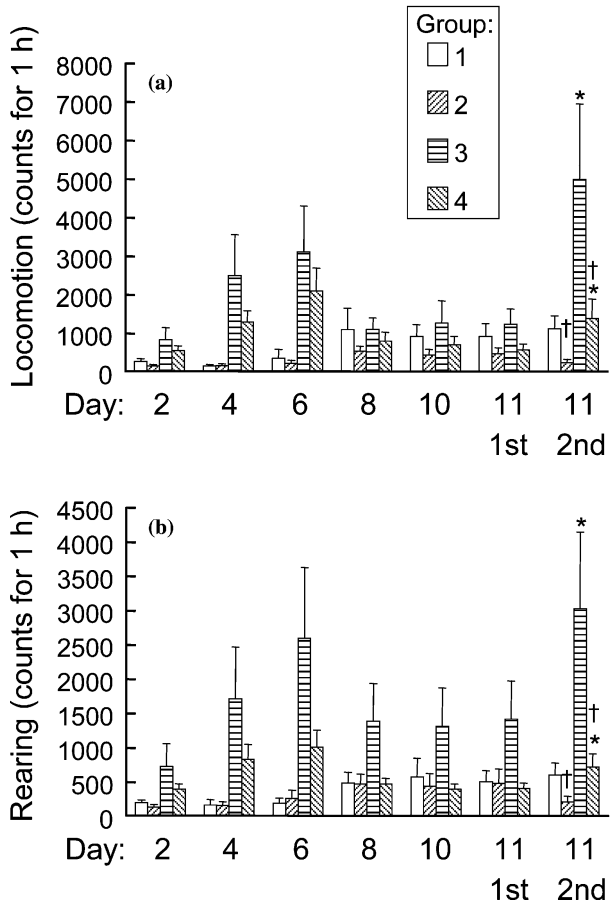

Fig. 2. Horizontal locomotor activity (a) and vertical rearing (b) in mice. Each column indicates total activity counts for 1 h. On Day 11, a single methamphetamine challenge induced significant locomotor activity and rearing in sensitized mice (Groups 3 and 4), compared with control animals (Groups 1 and 2) (*, two-way ANOVA, $F(1,44) = 5.981$, $P < 0.05$ and $F(1,44) = 6.477$, $P < 0.05$ for locomotion and rearing, respectively). Clorgyline treatment significantly decreased methamphetamine-induced hyperactivity (both locomotion and rearing) (†, two-way ANOVA, $F(1,44) = 4.774$, $P < 0.05$ and $F(1,44) = 5.507$, $P < 0.05$ for locomotion and rearing, respectively). The values are shown as means ± S.E.M. ($n = 12$ each). 1st/2nd = 1st/2nd measurement of locomotion and rearing (see Fig. 1).

$P < 0.001$, respectively), but increased them in the thalamus and hypothalamus ($F(1,44) = 19.062$, $P < 0.001$). The tissue content of homovanillic acid (HVA) was also significantly decreased ($F(1,44) = 30.471$, $P < 0.001$, $F(1,44) = 90.838$, $P < 0.001$, and $F(1,44) = 66.294$, $P < 0.001$ for the cerebral cortex, the striatum and accumbens, and the thalamus and hypothalamus, respectively). The tissue content of 3-methoxytyramine (3-MT) was increased in all the regions tested ($F(1,44) = 29.391$, $P < 0.001$, $F(1,44) = 91.214$, $P < 0.001$, and $F(1,44) = 32.755$, $P < 0.001$ for the cerebral cortex, the striatum, and the thalamus and hypothalamus, respectively). The tissue content of norepinephrine but not its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) significantly increased after repeated clorgyline treatment in all the regions tested ($F(1,44) = 52.781$, $P < 0.001$, $F(1,44) = 42.138$, $P < 0.001$, and $F(1,44) = 40.635$, $P < 0.001$ for the cerebral cortex, the striatum, and the thalamus and hypothalamus, respectively). The tissue content of 5-HT ($F(1,44) = 17.499$, $P < 0.001$, $F(1,44) = 33.784$, $P < 0.001$, and $F(1,44) = 38.940$, $P < 0.001$, respectively), and its metabolite 5-hydroxyindolacetic acid (5-HIAA) ($F(1,44) = 32.654$, $P < 0.001$, $F(1,44) = 9.852$, $P < 0.05$, and $F(1,44) = 49.239$, $P < 0.001$ for the cerebral cortex, the region of the striatum, and the thalamus and hypothalamus, respectively), significantly increased and decreased after repeated clorgyline treatment in all areas of the brain tested, respectively.

Apparent Monoamine Turnover

In the present study, the ratio of major metabolite to corresponding monoamine was used as an index of monoamine turnover (Fig. 3), using the tissue contents shown in Table II. As for serotonin metabolism, the ratio of 5-HIAA/5-HT is a good index of apparent serotonin turnover (17). In the cerebral cortex (Fig. 3a), the ratios of DOPAC/DA, HVA/DA, MHPG/NE, and 5-HIAA/5-HT significantly decreased after clorgyline treatment (Groups 2 and 4 vs. Groups 1 and 3; one-way ANOVA, $F(1,44) = 50.808$, $P < 0.001$, $F(1,44) = 30.398$, $P < 0.001$, $F(1,44) = 8.623$, $P < 0.01$, and $F(1,44) = 89.043$, $P < 0.001$, respectively). In contrast, the ratio of 3-MT/DA significantly increased ($F(1,44) = 64.876$, $P < 0.001$). The METH treatment significantly increased the apparent overall dopamine turnover (i.e., HVA/DA), compared with control groups (Group 3 vs. Groups 1 and 4 vs. Group 2, one-way ANOVA, $F(1,44) = 12.302$, $P < 0.01$).

In the striatum + accumbens (Fig. 3b), the ratios of DOPAC/DA, HVA/DA, MHPG/NE, and 5-HIAA/5-HT significantly decreased after clorgyline treatment (Groups 2 and 4 vs. Groups 1 and 3; one-way ANOVA, $F(1,44) = 40.764$, $P < 0.001$, $F(1,44) = 99.947$, $P < 0.001$, $F(1,44) = 26.128$, $P < 0.001$, and $F(1,44) = 27.506$, $P < 0.001$, respectively). In contrast, the ratio of 3-MT/DA significantly increased ($F(1,44) = 22.355$, $P < 0.001$).

In the thalamus and hypothalamus (Fig. 3c), the ratios of HVA/DA, MHPG/NE, and 5-HIAA/5-HT significantly decreased after clorgyline treatment (Groups 2 and 4 vs. Groups 1 and 3; one-way

Table II. Tissue Contents of Monoamines and Their Metabolites in Brain Regions of the Methamphetamine-sensitized Mice (Day 11)

	DA	DOPAC	3-MT	HVA
Cerebral cortex				
Group 1	4.25 ± 0.48	0.319 ± 0.042	0.384 ± 0.057	0.495 ± 0.074
Group 2	4.65 ± 0.55	0.072 ± 0.013[b]	0.879 ± 0.114[b]	0.144 ± 0.031[b]
Group 3	3.49 ± 0.47	0.310 ± 0.030	0.359 ± 0.055	0.538 ± 0.063
Group 4	3.96 ± 0.52	0.075 ± 0.014[b]	0.768 ± 0.092[b]	0.246 ± 0.057[b]
Striatum + accumbens				
Group 1	10.95 ± 1.32	1.099 ± 0.272	0.839 ± 0.103	1.378 ± 0.151
Group 2	13.52 ± 1.43	0.125 ± 0.026[b]	1.807 ± 0.109[b]	0.393 ± 0.059[b]
Group 3	11.10 ± 1.34	0.927 ± 0.100	0.656 ± 0.030	1.256 ± 0.106
Group 4	14.64 ± 2.07	0.189 ± 0.025[b]	1.660 ± 0.139[b]	0.319 ± 0.055[b]
Thalamus + hypothalamus				
Group 1	0.71 ± 0.07	0.175 ± 0.026	0.054 ± 0.015	0.273 ± 0.040
Group 2	0.74 ± 0.08	0.308 ± 0.047[b]	0.151 ± 0.023[b]	0.066 ± 0.020[b]
Group 3	0.74 ± 0.07	0.189 ± 0.020	0.069 ± 0.015	0.321 ± 0.035
Group 4	0.82 ± 0.08	0.369 ± 0.043[b]	0.177 ± 0.018[b]	0.058 ± 0.011[b]
	NE	MHPG	5-HT	5-HIAA
Cerebral cortex				
Group 1	1.06 ± 0.08	1.701 ± 0.351	1.93 ± 0.23	0.576 ± 0.076
Group 2	1.91 ± 0.13[b]	1.667 ± 0.296	3.23 ± 0.35[b]	0.224 ± 0.044[b]
Group 3	1.01 ± 0.06	1.771 ± 0.324	1.88 ± 0.21	0.506 ± 0.058
Group 4	1.76 ± 0.15[b]	1.742 ± 0.312	3.22 ± 0.42[b]	0.210 ± 0.041[b]
Striatum + accumbens				
Group 1	1.39 ± 0.13	0.772 ± 0.129	1.45 ± 0.14	1.277 ± 0.350
Group 2	2.63 ± 0.23[b]	0.642 ± 0.104	2.24 ± 0.21[b]	0.496 ± 0.078[a]
Group 3	1.37 ± 0.14	0.774 ± 0.112	1.34 ± 0.14	0.886 ± 0.104
Group 4	2.63 ± 0.25[b]	0.651 ± 0.072	2.38 ± 0.13[b]	0.481 ± 0.061[a]
Thalamus + hypothalamus				
Group 1	4.74 ± 0.35	1.058 ± 0.315	3.58 ± 0.40	1.200 ± 0.133
Group 2	8.74 ± 0.56[b]	0.536 ± 0.085	7.04 ± 0.74[b]	0.492 ± 0.074[b]
Group 3	4.95 ± 0.26	0.705 ± 0.105	3.63 ± 0.28	1.212 ± 0.104
Group 4	8.20 ± 0.89[b]	0.525 ± 0.077	7.37 ± 0.75[b]	0.537 ± 0.070[b]

Note: The brains were dissected 1 h after the methamphetamine challenge (1 mg/kg, i.p.). Values are expressed as nanograms per milligram of wet tissue (mean ± S.E.M., $n = 12$). For the experimental protocol for Groups 1–4, see Table I.
DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; 3-MT, 3-methaoxytyramine; HVA, homovanillic acid, NE, norepinephrine; MHPG, 3-methoxy-4-hydroxyphenylglycol; 5-HT, 5-hydroxytryptamine (serotonin); 5-HIAA, 5-hydoxyindolacetic aicd. [a]$P < 0.01$, [b]$P < 0.001$, compared with the corresponding control group (no clorgyline treatment) (one-way ANOVA).

ANOVA, $F(1,44) = 28.542$, $P < 0.001$, $F(1,44) = 5.352$, $P < 0.05$, and $F(1,44) = 311.506$, $P < 0.001$, respectively). In contrast, the ratios of DOPAC/DA and 3-MT/DA significantly increased ($F(1,44) = 18.017$, $P < 0.001$ and $F(1,44) = 17.262$, $P < 0.001$, respectively).

DISCUSSION

The results of the present study indicated that repeated administration of clorgyline, known as a MAO-A inhibitor (11), significantly inhibited METH-induced behavioral sensitization in mice. The inhibition was significant in terms of horizontal locomotion and vertical rearing (Fig. 2). There was a possibility that the repeated treatment resulted in sedation. However, as shown in Fig. 2, treatment with clorgyline had no effect on spontaneous locomotion and rearing on Days 8, 10, and 11 (first), indicating no sedative effect of repeated treatment.

It was reported that the tissue content of 3-MT, an intermediate metabolite of dopamine formed by the COMT pathway, did not change in mice treated repeatedly with METH (1 mg/kg, i.p., once per day for five consecutive days) in the striatum and accumbens (16). On the other hand, a significant decrease in the tissue content of DOPAC was reported, suggesting a selective inhibition by METH of the MAO pathway for dopamine metabolism in the striatum and accumbens (16). In the present study, after repeated METH treatment, the mice were exposed to repeated clorgyline treatment followed by the final challenge with a single administration of METH (Table I). In all the regions examined, repeated treatment with clorgyline significantly increased the tissue content of 3-MT (Groups 2 and 4 vs. Groups 1 and 3, Table II). This suggested that,

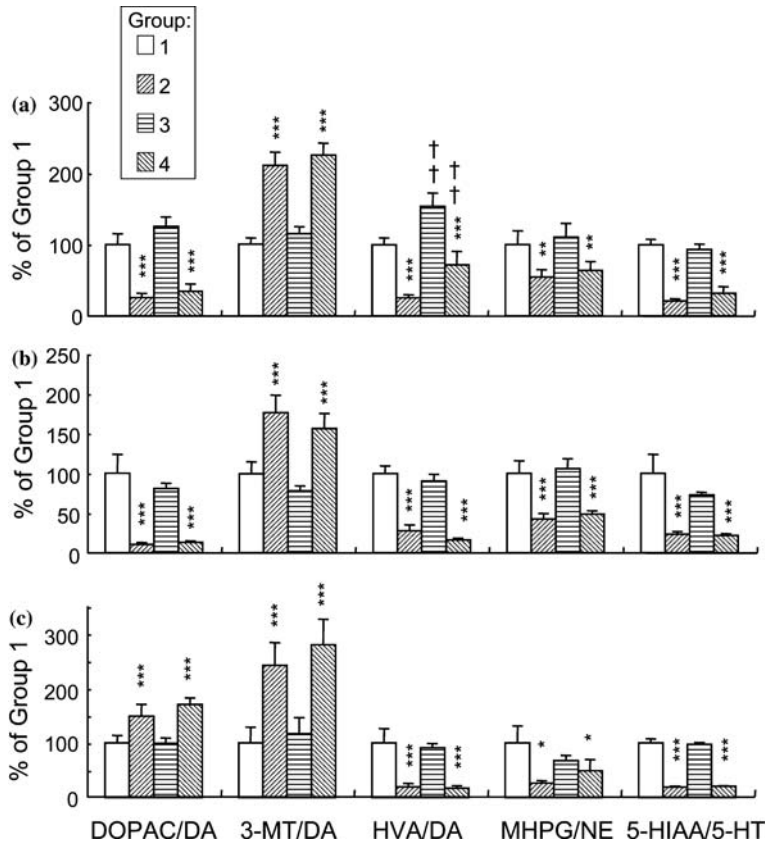

Fig. 3. Apparent monoamine turnover in the cerebral cortex (a), the striatum + accumbens (b), and thalamus + hypothalamus (c) of the mice 1 h after the final methamphetamine injection on Day 11. Each column represents the mean ± S.E.M. ($n = 12$). The MHPG, 3-methoxy-4-hydroxyphenylglycol; 3-MT, 3-methoxytyramine; NE, norepinephrine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid, DA, dopamine; 5-HIAA, 5-hydroxyindolacetic acid; 5-HT, serotonin. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, significantly different change in apparent monoamine turnover after clorgyline treatment (Groups 2 and 4), compared with control animals (Groups 1 and 3) (one-way ANOVA); $\dagger\dagger P < 0.01$, compared with control group (Group 1 or 2, one-way ANOVA).

with or without repeated METH treatment, brain dopamine, which is not metabolized by MAO-A after repeated clorgyline treatment was, in turn, exposed to COMT, another dopamine-metabolizing enzyme.

The enzyme COMT exists as two forms, membrane-bound and soluble, generated from one gene with two distinct promoters (for review, see Ref. (9)). In rodents, the COMT protein appears mostly in the soluble form. In the rat brain, it is located mainly in astrocytic processes as an intracellular enzyme (18). The glial COMT appears to be important to metabolize the dopamine released and to terminate dopaminergic transmission, since cultured astrocytes express dopamine uptake components (19,20). The control by COMT of the dopamine concentration in the synaptic cleft might become significant when a higher concentration of dopamine is released and not metabolized by MAO.

In the present study, it should be noted that, in the cerebral cortex, repeated METH treatment significantly increased the apparent overall dopamine turnover (i.e., ratio of HVA to dopamine), compared with control groups (Group 3 vs. Group 1, and Group 4 vs. Group 2, Fig. 3a). The activity of COMT in the cerebral cortex might contribute to the phenomenon, since (i) cortical MAO-A activity is inhibited by repeated METH treatment or by a combination of METH and clorgyline treatment (Fig. 3a) and (ii) dopamine metabolism in the cerebral cortex is more sensitive in terms of COMT than that in the striatum or hypothalamus (10). It is suggested that the dopamine released in the cerebral cortex by a single METH challenge was largely metabolized by COMT after clorgyline treatment, resulting in the decrease in locomotor activity (Fig. 2, second measurement on Day 11). The mechanism remains unresolved and

should be clarified in terms of changes in the tissue levels of the COMT gene and/or protein.

Taken together, our results indicated that clorgyline treatment effectively inhibits METH-induced behavioral sensitization in mice via an alteration of dopamine turnover via the COMT pathway in the cerebral cortex. We propose here the possibility that clorgyline treatment up-regulates the activity of COMT in the cerebral cortex and metabolizes dopamine effectively, leading to the suppression of METH-induced behavioral sensitization.

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