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CHANGES IN MONOAMINE OXIDASE ACTIVITY IN MOUSE BRAIN ASSOCIATED WITH *d*-METHAMPHETAMINE DEPENDENCE AND WITHDRAWAL

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Abstract—The long-term effects of *d*-methamphetamine (MP, 5 mg/kg) on brain mitochondrial monoamine oxidase (MAO) activity were studied in mice given MP intraperitoneally daily for 4 weeks. The MAO activities decreased when serotonin (5-HT) and dopamine (DA) were used as substrates. A marked elevation in MAO activity was seen during MP withdrawal when 5-HT, DA, β-phenylethylamine (β-PEA) and norepinephrine (NE) were used as substrates. The kinetics of MAO showed a significant decrease in K_m values, but no significant change in V_{max} values during MP withdrawal, despite the presence of NE. The K_m and V_{max} values increased when NE was the substrate. Inhibition of MAO by MP or its metabolites (amphetamine, *p*-hydroxyamphetamine and *p*-hydroxymethamphetamine) increased with the use of the following substrates in the order: DA, 5-HT, NE and β-PEA.

Repeated administration of amphetamine (AP†) or methamphetamine (MP) has been reported to enhance behavioral responses such as stereotypy and locomotor activity [1–3]. It is also well known that the effects of AP and MP can be modified by repeated administration, such that tolerance or reverse tolerance can develop [4–6]. However, the biochemical basis of this central stimulation is still uncertain. Recently, it has been reported that treatment with repeated, large doses of MP can inhibit the activity of both neostriatal tyrosine hydroxylase and tryptophan hydroxylase, although the mechanism of this inhibition is not known [7, 8]. Further, while it is known that AP and MP inhibit monoamine oxidase (MAO), which catalyses the oxidation of biogenic amines such as serotonin (5-HT) and catecholamines in brain mitochondria both *in vivo* and *in vitro*, it is not known whether this inhibition is related to the central stimulatory effects of these drugs. In the present paper, we describe the MAO activity in the brains of mice during repeated administration of *d*-methamphetamine (MP) and during withdrawal from chronic MP treatment.

MATERIALS AND METHODS

dd-Strain mice (20–30 g) were used in all experiments. The mice were housed in temperature-controlled animal quarters, on a circadian cycle of 12 hr light and 12 hr dark. The animals were fed *ad lib.* with food and water. The mice were divided into three groups. The first group (control) was given only saline 0.9%. The second group (MP-treated group) was injected with *d*-methamphetamine (5 mg/kg, i.p. dissolved in saline) daily for 4 weeks. The third group (MP-withdrawn group) was injected with *d*-methamphetamine daily for 4 weeks which was subsequently withdrawn for 3 weeks. The mice were killed by decapitation 24 hr after the last dose and their brains were quickly removed and homogenized in 10 vol. of 0.32 M sucrose solution (previously adjusted to pH 7.4 with 0.5 M $NaHCO_3$). The mitochondrial fractions were prepared by differential centrifugation, as described earlier [9]. The mitochondria were washed twice by resuspension in 0.32 M sucrose solution and were used as the enzyme preparations. All operations were carried out at 4°. The contents of MP and AP in the mitochondrial preparations were determined by GLC and GLC–mass spectrometry.

The MAO activity was measured using the labeled substrates, [^{14}C]5-HT (5-HT), [^{14}C]β-phenylethylamine (β-PEA), [^{14}C]dopamine (DA), and [^{14}C]norepinephrine (NE), as described earlier [10]. The incubation medium contained a suitable amount of the enzyme preparation (25–100 μg protein) to give a linear reaction for at least 40 min in a total volume of 225 μL of phosphate buffer, pH 7.4. The reaction was started by adding 25 μL of labeled substrate, and incubation was carried out for 30 min at 37°. The reaction was then stopped by adding 2 M HCl. The products of the reaction were extracted with 2 mL of benzene-ethyl acetate (1:1, v/v). Ten milliliters of Triton X-100-toluene scintillation liquid were added to 1.0 mL samples of the extract, and their radioactivities were measured by a Tri-carb Liquid Scintillation Spectrometer. Specific MAO activity

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† Abbreviations: MAO, monoamine oxidase; 5-HT, serotonin; DA, dopamine; NE, norepinephrine; β-PEA, β-phenylethylamine; MP, (*d*-)methamphetamine; AP, amphetamine; OH-MP, *p*-hydroxymethamphetamine; OH-AP, *p*-hydroxyamphetamine.

was expressed as nmol/min/mg of protein. In the case where NE was used as a substrate, the incubation mixture consisted of 50 μL of the mitochondrial preparations, 0.2 mol ascorbic acid and phosphate buffer, pH 7.4, in a total volume of 225 μL. The reaction was started by adding 25 μL of labeled NE, and the mixture was incubated at 37° for 30 min. The reaction was stopped by adding 50 μL each of 0.25 M $ZnSO_4$ and 0.2 M $Ba(OH)_2$. The NE was separated from its deaminated metabolites, which were then eluted with 5 mL of water into glass scintillation counting vials containing 15 mL of Triton X-100-toluene scintillation liquid. Radioactivity was determined by a Tricarb Liquid Scintillation Spectrometer.

For the analysis of MAO inhibition or activity, the substrate concentrations used were 200 μM 5-HT, 10 μM β-PEA, 200 μM DA and 200 μM NE.

To determine the relationship between MAO activity and the amount of MAO in the mitochondria of rat brain, the titration experiment was performed with clorgyline (for determination of the content of A-form MAO) and deprenyl (for determination of the content of B-form MAO) [11, 12]. Various amounts of enzyme were preincubated with inhibitor at 37° for 1 hr in a total volume of 275 μL of phosphate buffer, pH 7.4. As a control, enzyme was preincubated in the same way, but in the absence of an inhibitor. After preincubation, 25 μL of labeled substrate was added to estimate MAO activity. The inhibitor concentrations used were 1×10^{-8} M clorgyline with 5-HT as a substrate and 5×10^{-8} M deprenyl with β-PEA.

In investigating the effects of MP and its metabolites on MAO activity *in vitro*, enzyme was preincubated for 20 min at 25° with the reagents at a concentration of 1 mM to 1 μM, before adding the substrates. The remaining MAO activity was measured after the substrates were added.

The protein concentrations of the enzyme preparations were measured according to the method of Lowry *et al.* [13], using bovine serum albumin as the standard. The protein concentration of enzyme preparations was adjusted to 1.0 mg/mL.

d-Methamphetamine-HCl (MP) and ephedrine-HCl were purchased from Dainippon Pharmaceutical Co. (Osaka, Japan). *p*-Hydroxymethamphetamine (OH-MP) sulfate and *p*-hydroxyamphetamine (OH-AP) oxalate were prepared from *p*-methoxyphenyl acetone according to the method of Buzas and DuFour [14]. Amphetamine sulfate was prepared according to the method of Magidson and Garkusha [15]. The purities of the products were checked by GLC and GLC–mass spectrometry. Radiochemical substrates: hydroxytryptamine binoxalate, 5-[2-^{14}C]-5-HT (47 mCi/mmol); dihydroxyphenylethylamine hydrobromide, 3,4-[8-^{14}C]DA (46 mCi/mmol); phenylethylamine hydrochloride, β-[ethyl-1-^{14}C]β-PEA (48 mCi/mmol); and norepinephrine hydrochloride, DL-[7-^{14}C]NE (54.8 mCi/mmol) were purchased from New England Nuclear (Boston, MA, U.S.A.). All other chemicals were obtained from Wako Pure Chemical Industries (Osaka, Japan).

RESULTS

Changes in MAO activity in the mitochondria of mouse brain after administration of MP

The MAO activity in brain mitochondria was measured using 5-HT, DA, β-PEA and NE as substrates following MP administration. Figure 1 shows that, when 5-HT was the substrate, MAO activities began to decrease gradually after the administration of MP (5 mg/kg), while when DA was used significant inhibition of MAO activity was observed in the first and fourth weeks of administration of MP. When β-PEA was the substrate, no marked changes in MAO activity were observed, but MAO activities increased in the first, second and fourth weeks of administration of MP when NE was the substrate. Notably, marked increases in MAO activity were observed with all substrates upon withdrawal after chronic administration of MP (5 mg/kg, i.p.) daily for 4 weeks.

K_m *and* V_{max} *values of MAO in the mitochondria of mice*

We compared the enzyme preparations of the three groups in order to investigate the relationship between differences in MAO activity in the fourth week of repeated administration of saline or MP, and the third week of withdrawal. The K_m and V_{max} values for the control (mitochondrial preparations administered with saline in the fourth week or the third week after stopping the administration of saline), MP-treated (mitochondrial preparation administered with MP in the fourth week) and MP-withdrawn (mitochondrial preparations in the third week after MP withdrawal) groups were determined from Lineweaver–Burk double reciprocal plots of values obtained from the graphic representation of the kinetics data. Table 1 shows the results with 5-HT, DA, β-PEA and NE as substrates. In the case of MP-treated mice, the K_m and V_{max} values decreased significantly compared to controls when 5-HT and DA were substrates. When NE was the substrate, the K_m and V_{max} values increased significantly. When the brain mitochondrial preparations of MP-withdrawn mice were used, the K_m values decreased significantly compared to controls when the substrates were 5-HT, DA and β-PEA, although the V_{max} values were almost identical. Both the K_m and V_{max} values increased markedly when the substrate was NE.

Effects of the MAO inhibitors, clorgyline and deprenyl, on MAO in the brains of mice given MP

Using the mitochondrial preparations from MP-treated and MP-withdrawn mouse brains, the inhibitory effects of various concentrations of clorgyline and deprenyl were compared with those of controls. When the substrate was 5-HT, the MAO activity was highly sensitive to clorgyline, while with β-PEA as the substrate, the MAO activity was less sensitive. In the case of incubation with deprenyl, MAO activities showed the most sensitivity to β-PEA oxidation, and the least sensitivity to 5-HT oxidation. In the mitochondrial preparations from MP-treated and MP-withdrawn mice, the inhibition curves for clorgyline and deprenyl were almost identical to those for the controls (Fig. 2).

To determine the relationship between MAO activity and the amounts of MAO in the mitochondria of mouse brain, titration experiments were performed

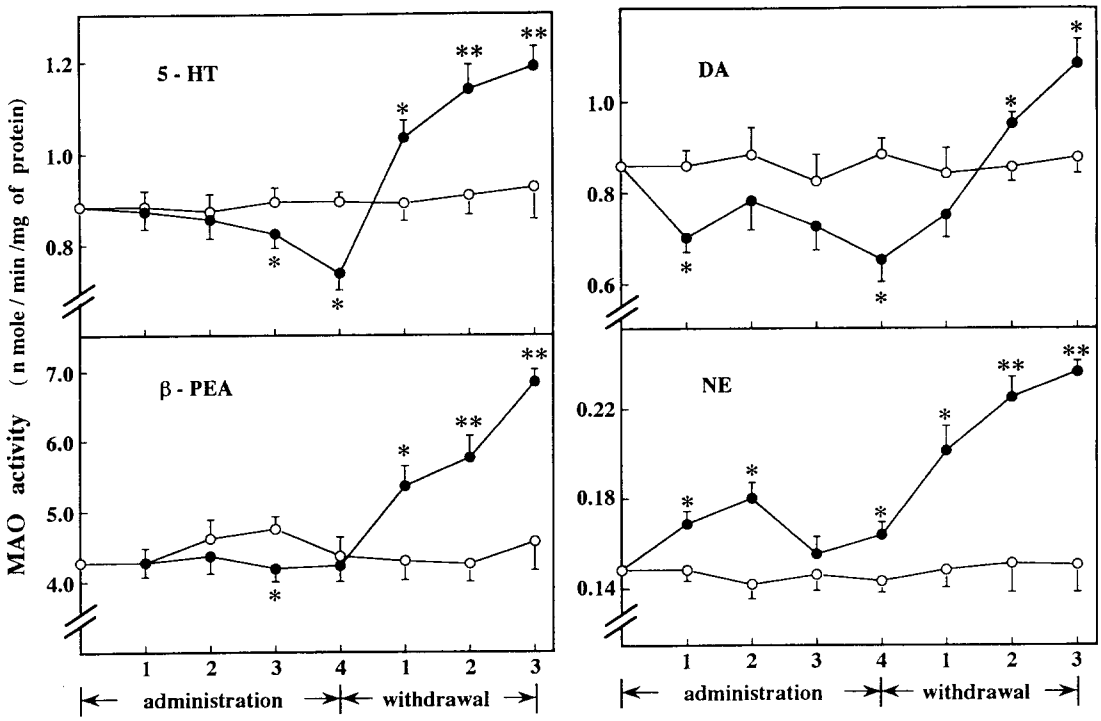

Fig. 1. Changes in MAO activity in mitochondria of mouse brain after administration (4 weeks) of MP and withdrawal (3 weeks). MAO activity was measured using labeled substrates. Specific activity is expressed as nmol of products formed/min/mg of protein. Each point represents the mean ± SE of the enzyme activity in five mice. (●) MP administration (5 mg/kg, i.p.), (○) saline only.

Table 1. The V_{max} and K_m values of mitochondrial MAO of mice in each group

	Control*		MP-treated*		Control†		MP-withdrawn†	
	K_m	V_{max}	K_m	V_{max}	K_m	V_{max}	K_m	V_{max}
5-HT	117 ± 12	2.12 ± 0.07	76 ± 8§	1.78 ± 0.05‡	120 ± 3	2.00 ± 0.09	84 ± 4§	2.24 ± 0.07
DA	249 ± 13	1.25 ± 0.05	226 ± 3‡	1.10 ± 0.04‡	258 ± 20	1.19 ± 0.08	198 ± 10§	1.29 ± 0.08
β-PEA	9.3 ± 0.4	4.87 ± 0.12	8.2 ± 0.8	4.97 ± 0.11	10.1 ± 1.1	5.32 ± 0.24	6.6 ± 0.3§	5.02 ± 0.17
NE	253 ± 51	1.20 ± 0.08	380 ± 48§	1.51 ± 0.11‡	260 ± 43	1.18 ± 0.03	793 ± 100§	2.67 ± 0.33§

* Control and MP-treated: the K_m and V_{max} values of MAO in the brains of mice administered saline and MP (5 mg/kg, i.p.) in the fourth week.

† Control and MP-withdrawn: The K_m and V_{max} values of MAO in the brains of mice in the third week of withdrawal after repeated administration of saline or MP (5 mg/kg, i.p.) daily for 4 weeks.

Each value represents the mean ± SE in five mice.

K_m: μM, V_{max}: nmol/min/mg of protein.

‡ $P < 0.01$, § $P < 0.001$ vs control.

with clorgyline and deprenyl. Clorgyline and deprenyl inhibit MAO irreversibly at a ratio of 1:1, i.e. the amount of enzyme inhibited was equal to the amount of inhibitor added on a molar basis. With the mitochondrial preparations obtained from control, MP-treated and MP-withdrawn mouse brains, about 32 μL of enzyme preparation was titrated with 0.3 pmol of clorgyline with 5-HT as the substrate. While, with β-PEA as substrate, about 11 μL of the same enzyme preparations was titrated with 0.9 pmol of deprenyl.

Effects of MP, AP, OH-MP and OH-AP on MAO activity in vitro

To determine the mechanism of inhibition of MAO activity by MP and its metabolites, AP, OH-MP and OH-AP, the effects of various concentrations of these reagents on MAO in mouse brain mitochondria *in vitro* were studied using 5-HT, DA, β-PEA and NE as substrates. As can be seen in Fig. 3, MAO activities decreased with increased concentrations of these reagents for all substrates tested. Particularly, when DA and 5-HT were used

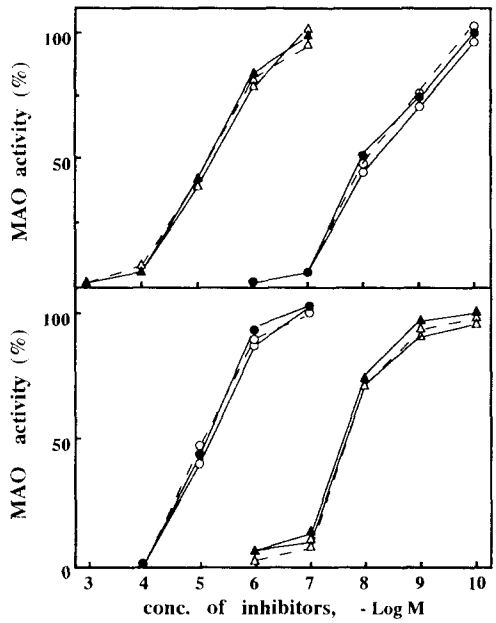

Fig. 2. Effects of clorgyline and deprenyl on MAO in brains of mice administered MP. After incubation at 37° for 20 min with various concentrations of clorgyline (upper) and deprenyl (lower), MAO activity was determined with 5-HT and β-PEA as substrates at 37° for 20 min. The results are means of triplicate assays. Enzyme preparations are from mouse brains after repeated administration of MP [(●) 5-HT, (▲) β-PEA], MP withdrawal [(○) 5-HT, (△) β-PEA] and saline [(○) 5-HT, (△) β-PEA].

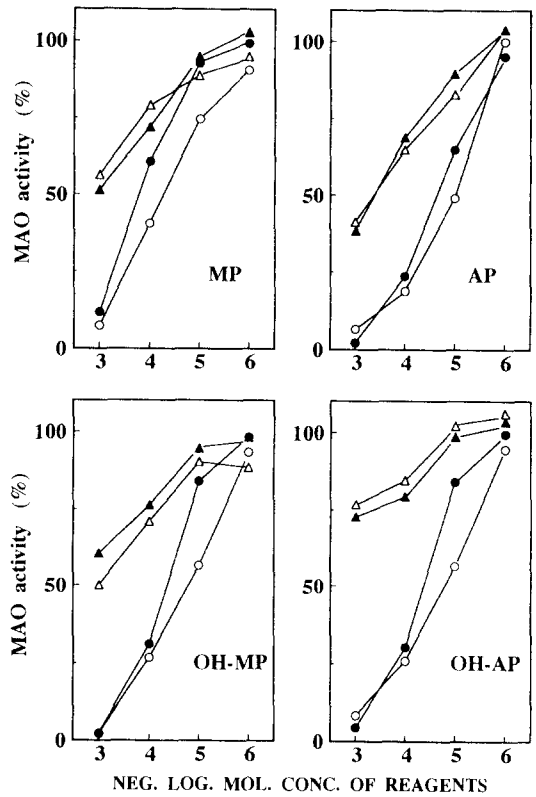

Fig. 3. Effects of MP and its metabolites on MAO activity in mouse brain mitochondria. After incubation at 25° for 20 min with various concentrations of these reagents, MAO activity was determined with 200 μM 5-HT (●), 200 μM DA (○), 10 μM β-PEA (▲) and 200 μM NE (△) as substrates at 37° for 20 min. The mean control values for MAO activity in mitochondria were 0.70, 0.41, 1.62 and 0.40 nmol/min/mg protein with 5-HT, DA, β-PEA and NE as substrates, respectively. The results are means of triplicate assays.

as substrates, MAO was inhibited more by MP than by β-PEA and NE. Similar results were obtained using AP, OH-MP and OH-AP.

Inhibition of mouse brain mitochondrial MAO by MP, AP, OH-MP and OH-AP

The kinetics of the inhibition of MAO by the addition of these reagents (MP, AP, OH-MP and OH-AP) was investigated using Lineweaver–Burk double-reciprocal plots. All of these reagents are competitive inhibitors of mouse brain mitochondrial MAO with 5-HT, DA, β-PEA and NE as substrates (data not shown). The respective K_i values were calculated from the apparent Michaelis constants, and the K_m and K_i values are presented in Table 2. The K_i values for these reagents were lower than the K_m values calculated using Lineweaver–Burk plots, with 5-HT, DA and NE. In contrast, the K_i values for these reagents were higher than the K_m values with β-PEA as substrate. The K_i values for AP were much lower than those for MP, OH-MP and OH-AP for all substrates tested.

DISCUSSION

It is known that MP competitively inhibits MAO, and that it is more potent *in vitro* for type A MAO than for type B MAO. This has been thought to produce some changes in MAO *in vivo*, following repeated administration of MP. We previously reported that the activities of type A and B MAO in the mitochondria and synaptosomes in the brains of monkeys administered MP (2 mg/kg, i.m. daily for 7 days) showed a decrease in K_m and V_{max} values when the substrates were 5-HT and β-PEA, while in the synaptosomes a significant increase in the K_m and V_{max} values was observed when 5-HT and DA were the substrates [16]. The present study gave similar results.

The MAO activity in mouse brain mitochondria began to decrease gradually after chronic administration of MP (5 mg/kg, daily for 4 weeks), with 5-HT as a substrate, while significant inhibition of MAO activity was observed in the first and fourth week when DA was the substrate. By contrast, MAO activity increased when NE was the substrate. In order to determine whether the changes in MAO activity were due to a change in the molecular amount of MAO, a titration experiment with clorgyline (A-form MAO specific) and deprenyl (B-form MAO specific) was performed using 5-HT (for A-form MAO) and β-PEA (for B-form MAO) as

Table 2. Substrate and inhibitor constants for mouse brain mitochondrial MAO

	K_m (μM)	K_i (μM) values toward:			
		MP	AP	OH-MP	OH-AP
5-HT	117 ± 12	33.3 ± 5.2	4.5 ± 1.1	8.2 ± 1.9	8.2 ± 0.7
DA	249 ± 13	10.2 ± 1.8	2.0 ± 0.5	3.2 ± 0.3	3.2 ± 0.1
β-PEA	9.3 ± 0.4	83.7 ± 8.3	48.5 ± 5.7	108.9 ± 8.8	418.9 ± 20.1
NE	253 ± 51	47.6 ± 5.2	11.3 ± 3.3	28.3 ± 5.2	113.4 ± 8.7

All assays were performed in triplicate.

K_i values were calculated according to the method of Dixon and are expressed as means ± SE for three mouse brain preparations.

substrates. No significant changes in the titrations by clorgyline and deprenyl were observed for either group. Therefore, the changes in MAO activity were not due to changes in the number of MAO molecules. Analysis of MAO kinetics in each group showed a significant decrease in the K_m and V_{max} values for the MP-treated mice when the substrates were 5-HT and DA, while when NE was the substrate, we observed significant increases in both the K_m and V_{max} values. However, this increase was observed when the concentration of NE used was over 160 μM.

Similar results have been obtained with other enzymes using large doses of MP. Bakhit *et al.* [7] reported that the V_{max} value of the neostriatal tyrosine hydroxylase in rats markedly decreased after large, repeated doses of MP, although no change in the K_m value was observed. Trulson and Jacobs [17] reported that chronic administration of AP to cats produced a decrease in the V_{max} value of brain stem and forebrain tryptophan hydroxylase activity, with no change in the K_m value. These results indicate that chronic AP treatment decreases central serotonergic neuro-transmission via a rate-limiting enzyme in serotonin biosynthesis. Hotchkiss *et al.* [8] also reported that treatment with repeated, large doses of MP produced a decrease in tyrosine hydroxylase and tryptophan hydroxylase activity, while the activity of choline acetyltransferase and glutamate decarboxylase did not change. They suggested that this toxic effect cannot be attributed to generalized destruction of the neostriatum since it has only been observed in selected biogenic amine nerve terminals. Moreover, repeated administration of MP has been reported to enhance the reduction in neostriatal concentrations of DA, 5-HT and their metabolites as a consequence of a decrease in the activity of tyrosine hydroxylase and tryptophan hydroxylase. This depletion might also decrease the activity of MAO in various brain regions. These observations suggest that multiple, large doses of MP do not directly alter MAO by competitive binding, but instead cause conformational changes in the MAO molecule itself. This decrease in MAO activity may account for the observed serotonergic and dopaminergic neurotoxicity associated with repeated MP administration in mice. However, we still do not know what the mechanism is for the observed increases in MAO activation during the administration of MP, when NE was the substrate at a concentration greater than 160 μM, although the decrease in MAO activity was observed kinetically at a concentration lower than 160 μM. Further research will be necessary to investigate the relationship between ambulatory activity and neurochemical changes in catecholaminergic or serotonergic neurons in the brain.

By contrast, marked increases in MAO activity were observed with all substrates during withdrawal following the administration of MP. These increases were likewise not due to changes in MAO, as indicated by titration experiments using MAO inhibitors. However, K_m values in the brain mitochondrial MAO of MP-withdrawn mice decreased significantly compared with those of the control using 5-HT, DA and β-PEA as substrates, although the V_{max} values were almost identical. Also, both K_m and V_{max} values increased when NE was the substrate at concentrations greater than 90 μM.

Hirabayashi and Alam [5] reported that stereotyped behavior continued, once it had been established, even after an MP-free period of 2 months, and this behavior was considered to be almost irreversible. Woolverton *et al.* [18] reported that the destruction of nerve terminals by large doses of MP might persist for at least 6 months after the last injection of MP. Okada *et al.* [19] also reported that the concentration of DA and 5-HT decreased, while 3,4-dihydroxyphenylacetic acid, homovanillic acid and 5-hydroxyindole acetic acid increased up to 7 days after MP withdrawal. They suggested that the turnover rate of 5-HT and DA increased along with increases in tryptophan hydroxylase activity. These observations suggest that an increase in MAO activity underlines the observed changes in the levels of the monoamines.

During the chronic administration of MP, the activity of MAO decreased when the substrates were 5-HT and DA, but increased with NE oxidative deamination. During withdrawal after MP administration, the activity of MAO increased markedly with all substrates tested. Moreover, MAO activity was more sensitive to MP and its metabolites when DA was the substrate than when any other substrate was used. We suggest that there are fundamental differences between the three monoaminergic systems with regard to their capacity to adapt to chronic MP treatment.

REFERENCES

1. Peachey JE, Rogers B, Brien JF, Maclean A and Rogers D, Measurement of acute and chronic behavioral effects of methamphetamine in the mouse. *Psychopharmacology* **48**: 271–275, 1976.
2. Nelson LR and Ellison G, Enhanced stereotypies after repeated injections but not continuous amphetamines. *Neuropharmacology* **17**: 1081–1084, 1978.
3. Alam MR, Enhancement of motor-accelerating effect induced by repeated administration of methamphetamine in mice: involvement of environmental factors. *Jpn J Pharmacol* **31**: 897–904, 1981.
4. Segal DS, Weinberger SB, Cahill L and McCunney SJ, Multiple daily amphetamine administration: behavioral and neurochemical alterations. *Science* **207**: 904–907, 1980.
5. Hirabayashi M and Alam MR, Enhancing effect of methamphetamine on ambulatory activity produced by repeated administration in mice. *Pharmacol Biochem Behav* **15**: 925–932, 1981.
6. Schmidt CJ, Sonsa PK, Hanson GR, Peat NA and Gibb JW, Methamphetamine induced depression of monoamine synthesis in the rat: Development of tolerance. *J Neurochem* **44**: 852–855, 1985.
7. Bakhit C, Kwok YC and Gibb JW, Effects of methamphetamine on kinetic characteristics of neostriatal tyrosine hydroxylase. *Life Sci* **26**: 1815–1819, 1980.
8. Hotchkiss AJ, Morgan ME and Gibb JW, The long-term effects of multiple doses of methamphetamine on neostriatal tryptophan hydroxylase, tyrosine hydroxylase, choline acetyltransferase and glutamate decarboxylase activities. *Life Sci* **25**: 1373–1378, 1979.
9. Egashira T, Yamamoto T and Yamanaka T, Characteristics of mitochondrial and synaptosomal monoamine oxidase in monkey brain. *Jpn J Pharmacol* **34**: 211–219, 1984.
10. Egashira T, Kuroiwa Y and Kamijo K, Multiple catalytic sites of rat brain mitochondrial monoamine oxidase. *Arch Biochem Biophys* **191**: 714–718, 1978.
11. Egashira T, Ekstedt B, Kinemuchi H, Wiberg A and Oreland L, Molecular turnover numbers of different forms of mitochondrial monoamine oxidase in rat. *Med Biol* **54**: 272–277, 1976.
12. Egashira T and Yamanaka Y, Further studies on the synthesis of A-form monoamine oxidase. *Jpn J Pharmacol* **31**: 763–770, 1981.
13. Lowry OH, Rosebrough NJ, Farr AL and Randall RJ, Protein measurement with the Folin phenol reagent. *J Biol Chem* **193**: 265–275, 1951.
14. Buzas A and DuFour C, Preparation of 2-(*p*-hydroxyphenyl)-isopropyl methylamine. *Bull Soc Chem France* 139–140, 1941.
15. Magidson OY and Garkusha GA, The synthesis of 2-phenyl-isopropylamine (phenamine). *J Gen Chem* **11**: 339–343, 1941.
16. Egashira T, Yamamoto T and Yamanaka Y, Effects of *d*-methamphetamine on monkey brain monoamine oxidase, *in vivo* and *in vitro*. *Jpn J Pharmacol* **45**: 79–88, 1987.
17. Trulson ME and Jacobs BL, Chronic amphetamine administration to cats: behavioral and neurochemical evidence for decreased central serotonergic function. *J Pharmacol Exp Ther* **211**: 375–384, 1979.
18. Woolverton WL, Ricaurte GA, Forno LS and Seiden LS, Long term effects of chronic methamphetamine administration in rhesus monkeys. *Brain Res* **486**: 73–78, 1989.
19. Okada S, Morimasa T, Ikeda M, Nanba Y, Kaneyuki T and Shomori T, The effect of methamphetamine on the dopaminergic activities in the rat limbic areas. *Neuroscience* **11**: 232–233, 1985 (abstract in English).