Effect of Subchronic Treatment with Methamphetamine on Apomorphine-Induced Changes in Locomotor Activity in Mice

Hiroshi WATANABE and Michi-e TANIGUCHI
Research Institute for Wakan-yaku, Toyama Medical and Pharmaceutical University, Toyama 930-01, Japan
Accepted October 18, 1985

Abstract—Subchronic treatment with methamphetamine (3 mg/kg, s.c., twice daily for 14 days) attenuated hypomotility produced by a low dose of apomorphine (0.1 mg/kg, s.c.) and enhanced hypermotility induced by a high dose of apomorphine (3 mg/kg, s.c.) in mice. The treatment did not affect apomorphine-induced decrease in striatal DOPA accumulation following r-butyrolactone plus m-hydroxybenzylhydrazine, an L-amino acid decarboxylase inhibitor, administration. These results suggest that drug sensitivity of presynaptic dopamine receptors in the striatum may not be altered after subchronic methamphetamine treatment.

It has been well known that subchronic treatment with amphetamines induces enhanced responses to locomotion-increasing and stereotypy-producing effects of amphetamines in animals (for a review, see ref. 1). To investigate the mechanisms of behavioral enhancement, we examined effects of apomorphine on locomotor activity and striatal DOPA accumulation in mice pretreated with subchronic methamphetamine.

Male albino mice (ddY strain, Shizuoka Animal Center Lab., Shizuoka) weighing 22 to 28 g were pretreated with either methamphetamine (3 mg/kg, s.c.) or saline (0.1 ml/10 g, s.c.) twice daily for 14 days. These animals were injected with challenge doses of apomorphine (0, 0.05, 0.1, 1.0 and 3.0 mg/kg, i.p.) on the 4th day of the withdrawal, and locomotor activity including stereotyped motility was individually measured for 30 min in an activity cage (32 x 32 x 13 cm³) equipped with nine photodiodes on the floor.

Seven days after the measurement of locomotor activity, effects of apomorphine on striatal DOPA levels were evaluated in the mice pretreated with saline or methamphetamine. Mice were injected with apomorphine (0, 0.01, 0.05 or 0.1 mg/kg, s.c.), r-butyrolactone (GBL; 750 mg/kg, i.p.) and m-hydroxybenzylhydrazine (NSD-1015; 100 mg/kg, i.p.) every five min. The animals were sacrificed by decapitation 30 min after NSD-1015 treatment, and the striatum was rapidly isolated as reported previously (2). The paired striata were homogenized in 1 ml of 0.25 N perchloric acid containing 0.2 μM cysteine and 40 ng of 3,4-dihydroxybenzylamine (as an internal standard) and centrifuged at 10,000×g for 10 min. DOPA and catecholamines were extracted with alumina and assayed using HPLC with electrochemical detection (Bioanalytical Systems, Inc.) (2).

Apomorphine hydrochloride (Dainippon Seiyaku) and NSD-1015 (Sigma Chemical Co.) were dissolved in sterile saline containing 0.02% ascorbic acid. Methamphetamine hydrochloride (Dainippon Seiyaku) and GBL (Tokyo Kasei) were dissolved in sterile saline. Doses of methamphetamine and apomorphine are given in ferms of the salts. Data were analyzed by two way analysis of variance followed by Tukey's test for multiple comparison.

In the behavioral experiment, there were significant differences between pretreatments (F=11.4; df=1, 90; P<0.01) and between doses of apomorphine (F=42.0; df=4, 90; P<0.01). Subchronic treatment with methamphetamine caused an attenuation of hypomotility produced by a low dose of apomorphine (0.1 mg/kg) and an enhance-
ment of hypermotility induced by the highest dose of apomorphine (3 mg/kg) (Fig. 1).

Apomorphine produced a dose-dependent decrease in DOPA levels in the striata of mice pretreated with subchronic methamphetamine or saline, while there were no significant differences between subchronic methamphetamine- and salinetreated animals (Table 1).

It is known that a low dose of apomorphine produces hypomotility due to the stimulation of presynaptic DA receptors (3-5), whereas a high dose of apomorphine produces locomotor activation and stereotypy probably due to the stimulation of postsynaptic DA receptors in the mesolimbic as well as nigrostriatal DA regions (6-8). Our first behavioral finding that subchronic pretreatment with methamphetamine attenuated apomorphine-induced hypomotility suggests

Fig. 1. Effects of subchronic methamphetamine treatment (3 mg/kg, s.c., twice daily for 14 days) on locomotor activity changes produced by apomorphine in mice. Each column represents the mean±S.E.M. (n=10). a) P<0.05, b) P<0.01 vs. respective saline control. c) P<0.01 vs. the corresponding group pretreated with subchronic saline.

Table 1. Changes in apomorphine-induced decrease in DOPA levels of the striatum in mice pretreated with subchronic methamphetamine or saline

| Drug          | Subchronic treatment |
|---------------|----------------------|
|               | Saline               | Methamphetamine |
| Apomorphine (mg/kg, i.p.) |     |                     |
| 0             | 4.95±0.22            | 5.17±0.09        |
| 0.01          | 4.25±0.14*           | 4.32±0.18**      |
| 0.05          | 2.81±0.16**          | 3.38±0.34*       |
| 0.1           | 2.78±0.09**          | 2.95±0.32**      |
| NSD-1015 control | 1.49±0.09            | 1.55±0.11        |

Mice were sacrificed 30 min after the administration of m-hydroxybenzylhydrazine (NSD-1015; 100 mg/kg, i.p.). Apomorphine (0–0.1 mg/kg, s.c.) and γ-butyrolactone (750 mg/kg, i.p.) were administered 10 and 5 min before the administration of m-hydroxybenzylhydrazine, respectively. DOPA levels are μg/g wet tissue and represent the mean±S.E.M. (n=4–5). *P<0.05, **P<0.01 vs. respective values at 0 mg/kg of apomorphine.
that the pretreatment may induce hyposensitivity of presynaptic DA receptors in the mesolimbic DA regions and/or striatum. Electrophysiological study has shown that repeated administration of high doses of amphetamine produces a hyposensitivity of DA autoreceptors in the substantia nigra of the rat (9). Radioligand binding assays have detected a reduction in the number of presynaptic DA receptors in the striatum of rats after subchronic treatment with amphetamine (10). However, functional hyposensitivity of presynaptic DA receptors in the striatum was not confirmed in our study as reported in rats (11), whereas its possibility in the mesolimbic regions cannot be excluded. Enhancement of apomorphine-induced hypermotility may be seen through presynaptic as well as postsynaptic receptor mechanisms. Further studies are in progress to clarify sensitivity changes of presynaptic DA receptors in the mesolimbic regions.

References
1 Toru, M.: Central pharmacological actions of amphetamine and reversed tolerance phenomenon. In Pharmacology of Schizophrenia, p. 104–129, Chugai-Igaku Sha, Tokyo (1983) (in Japanese)
2 Watanabe, H.: Simple method for evaluation of stimulatory effect of drugs on presynaptic dopamine receptors in mice. J. Pharmacol. Methods 14, 41–47 (1985)
3 Carlsson, A.: Receptor-mediated control of dopamine metabolism. In Pre- and Postsynaptic Receptors, Edited by Usdin, E. and Bunney, W.E., Jr., p. 49–65, Marcel Dekker, New York (1975)
4 DiChiara, G., Porceddu, M.L., Vargiu, L., Argiolas, A. and Gessa, G.L.: Evidence for dopamine receptors mediating sedation in the mouse brain. Nature 264, 564–567 (1976)
5 Sumners, C., de Vries, J.B. and Horn, A.S.: Behavioral and neurochemical studies on apomorphine-induced hypomotility in mice. Neuropharmacology 20, 1203–1208 (1981)
6 Lassen, J.B.: Inhibition and potentiation of apomorphine-induced hypermotility in rats by neuroleptics. Eur. J. Pharmacol. 36, 385–393 (1976)
7 Pijenburg, A.J.J., Honig, W.M.M., Van Der Heyden, J.A.M. and Van Rossum, J.M.: Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity. Eur. J. Pharmacol. 35, 45–58 (1976)
8 Costall, B. and Naylor, R.J.: The role of telencephalic dopaminergic systems in the mediation of apomorphine-stereotyped behavior. Eur. J. Pharmacol. 24, 8–24 (1973)
9 Kamata, K. and Rebec, G.V.: Nigral dopaminergic neurons: differential sensitivity to apomorphine following long-term treatment with low and high doses of amphetamine. Brain Res. 321, 147–150 (1984)
10 Muller, P. and Seeman, P.: Presynaptic subsensitivity as a possible basis for sensitization by long-term dopamine mimetics. Eur. J. Pharmacol. 55, 149–157 (1979)
11 Conway, P.G. and Uretsky, N.J.: Role of striatal dopaminergic receptors in amphetamine-induced behavioral facilitation. J. Pharmacol. Exp. Ther. 221, 650–655 (1982)