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Dopamine Antagonists Can Inhibit Methamphetamine Sensitization, But Not Cocaine Sensitization, When Assessed by Ambulatory Activity in Mice

HISASHI KURIBARA AND YOSHITAKA UCHIHASHI

Division for Behavior Analysis, Behavior Research Institute, Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi 371, Japan

Abstract—The repeated subcutaneous administration of methamphetamine (2 mg kg^{-1}) and cocaine (10 mg kg^{-1}) at 3–4 day intervals induced sensitization to their ambulation-increasing effects in mice. Subcutaneous administration of SCH 23390 (*R*-(+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 0·003–0·03 mg kg^{-1}) and YM-09151-2 (*cis*-*N*-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide; 0·003–0·03 mg kg^{-1}), the selective dopamine D_1 and D_2 antagonists, respectively, reduced dose-dependently the acute ambulation-increasing effect of methamphetamine. The development of methamphetamine sensitization was inhibited when it was administered in combination with either SCH 23390 or YM-09151-2 in the repeated administration schedule. Although SCH 23390 (0·01–0·1 mg kg^{-1}) and YM-09151-2 (0·01–0·1 mg kg^{-1}) also reduced the ambulation-increasing effect of cocaine (10 mg kg^{-1}), neither drug inhibited the cocaine sensitization. Mice given cocaine with SCH 23390 (0·03 mg kg^{-1}) or YM-09151-2 (0·03 and 0·1 mg kg^{-1}) showed higher sensitivity than those given cocaine alone. The present results suggest that, although both the dopamine D_1 and D_2 antagonists reduce the acute stimulant effects of both methamphetamine and cocaine, they are only effective for inhibition of the methamphetamine sensitization. Mechanisms other than the dopaminergic system appear to be involved in the cocaine sensitization.

Amphetamines and cocaine show similar behavioural stimulant actions, increasing spontaneous motor activity and inducing stereotypy in animals and man. The repeated administration of these drugs elicits a sensitization to the behavioural stimulant action of individual drugs (Kilbey & Ellinwood 1977; Kilbey & Sannerud 1985; Demellweek & Goudie 1983; Kuribara & Hirabayashi 1985; Tadokoro & Kuribara 1986, 1990), as well as cross-sensitization to other stimulants (Kuribara & Hirabayashi 1985; Akimoto et al 1990; Hirabayashi et al 1991). It has been suggested that a change in dopaminergic transmission is involved in the sensitization to stimulants, in particular amphetamines, since antipsychotics inhibit it (Kuribara et al 1986; Robinson & Becker 1986; Asami et al 1987; Ujike et al 1989). However, the traditional antipsychotics show a less selective blockade of either the dopamine D_1- or D_2-receptor subtype.

The purpose of this study was to investigate the effects of the blockade of dopamine D_1 and D_2 receptors by SCH 23390 (*R*-(+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine) and YM-09151-2 (*cis*-*N*-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide), respectively, on the sensitization to the ambulation-increasing effect of methamphetamine and cocaine in mice.

Materials and Methods

Animals

Male mice of the dd strain (Institute of Experimental Animal Research, Gunma University School of Medicine), were used for the experiments when they were 6 weeks old, weighing 25–28 g. Animals were housed in groups of 10 in aluminium breeding cages (25 width, 15 depth, 15 height cm, with wooden-flake bedding) with free access to solid diet (MF: Oriental Yeast, Tokyo) and tap water throughout the experimental period. The breeding room was controlled for temperature (23 ± 2 C) and relative humidity (55 ± 3%), with a 12-h light-dark cycle; lights on at 0600 h.

Correspondence: H. Kuribara, Division for Behavior Analysis, Behavior Research Institute, Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi 371, Japan.

Apparatus

The measurement of ambulatory activity was carried out with a tilting-type ambulometer having ten bucket-like activity cages of 20 cm in diameter (SMA-10: O'Hara & Co., Tokyo). A slight tilt of the activity cage generated by the ambulation (locomotion) of the mouse was detected by any of three microswitches attached to the cage.

Drugs

The drugs used were methamphetamine HCl (Philopon: Dainippon Pharmaceuticals, Osaka), cocaine HCl (Takeda Chemicals, Osaka), SCH 23390 HCl (Research Biochemicals, Natick, MA) and YM-09151-2 (Yamanouchi Pharmaceuticals, Tokyo). YM-09151-2 was first dissolved in a very small amount of 0·1 M HCl, then diluted with physiological saline. Methamphetamine, cocaine and SCH 23390 were dissolved directly in saline. The concentration of each drug solution was adjusted so that each volume injected was 0·1 mL/10 g body weight. The doses of methamphetamine and cocaine, 2 and 10 mg kg^{-1} subcutaneously, respectively, were reported to be optimum doses for increase in the ambulation of dd mice, without producing a marked stereotypy (Hirabayashi et al 1977).

Experimental procedures

Eight groups of 10 mice each were given one of the following

5 times at 3–4 day intervals: saline alone, methamphetamine alone, combination of methamphetamine with SCH 23390 (0·003, 0·01 and 0·03 mg kg^{-1}) or with YM-09151-2 (0·003, 0·01 and 0·03 mg kg^{-1}). In the combined administration, the drugs were given simultaneously. The mouse's ambulatory activity was observed for 3 h after each administration. Four days after the final (5th) administration, methamphetamine alone was administered to all of these mice. The administration of methamphetamine to age-adjusted drug-naive mice was also carried out.

The other eight groups of 10 mice each were given one of the following 5 times at 3–4 day intervals: saline alone, cocaine alone, combination of cocaine with SCH 23390 (0·01, 0·03 and 0·1 mg kg^{-1}) or with YM-09151-2 (0·01, 0·03 and 0·1 mg kg^{-1}). The combined administration was carried out at the same time. The mouse's ambulatory activity was recorded for 1·5 h, because of a shorter action of cocaine than that of methamphetamine. Four days after the final (5th) administration, cocaine alone was administered to all of these mice. The administration of cocaine to age-adjusted drug-naive mice was also carried out.

Statistical analyses

The mean 3-h overall ambulatory activity counts were first analysed by analysis of variance. In the cases of significant variation, the individual mean values were compared by Dunnett's test. When P values were equal to or less than 0·05, they were considered to be significantly different.

Results

The combination of methamphetamine with SCH 23390 or YM-09151-2

As shown in Table 1, in the first administration (i.e. the administration to the drug-naive mice), both SCH 23390 and YM-09151-2 significantly and dose-dependently reduced the ambulation-increasing effect of methamphetamine. Thus, the activity counts following the combined administration of methamphetamine with SCH 23390 (0·003–0·03 mg kg^{-1}) and with YM-09151-2 (0·01 and 0·03 mg kg^{-1}) were significantly lower than after the administration of methamphetamine alone.

The repeated methamphetamine administration elicited a

Table 1. Mean overall ambulatory activity (count ± s.e.m.) for 3 h after the repeated administration of methamphetamine (2 mg kg^{-1}) in combination with SCH 23390 or YM-09151-2.

	Repeated administration					Methamphetamine
Drugs	1st	2nd	3rd	4th	5th	challenge
Methamphetamine alone	2197 ± 191	2692 ± 280	3147 ± 340*	3770 ± 354**	4259 ± 319**	5016 ± 404
Methamphetamine						
+SCH 23390 (0·003)	702 ± 143##	865 ± 155##	1364 ± 360*,##	2443 ± 532**,#	2291 ± 668**,##	3904 ± 898
+SCH 23390 (0·01)	526 ± 87##	756 ± 191##	829 ± 298##	1373 ± 556*,##	2460 ± 765**,##	4009 ± 783
+SCH 23390 (0·03)	96 ± 18##	58 ± 10##	180 ± 24##	143 ± 18##	142 ± 28##	1416 ± 274##
Methamphetamine						
+YM-09151-2 (0·003)	1609 ± 299	1959 ± 367	1898 ± 365##	2319 ± 397##	2267 ± 365,##	3945 ± 959
+YM-09151-2 (0·01)	304 ± 54##	699 ± 113*,##	622 ± 104*,##	735 ± 137*,##	600 ± 118*,##	2276 ± 536##
+YM-09151-2 (0·03)	136 ± 10##	92 ± 14##	84 ± 21##	153 ± 37##	254 ± 31##	2226 ± 257##
Saline	73 ± 22	80 ± 22	77 ± 22	106 ± 57	56 ± 20	2150 ± 416##
No drugs						2205 ± 189

Figures in parentheses give the dose of the drug in mg kg^{-1}. n = 10 in each group. * and ** $P < 0·05$ and 0·01, respectively, vs the first administration within each group in the repeated administration schedule (Dunnett's test). # and ## $P < 0·05$ and 0·01, respectively, vs the group administered methamphetamine alone (Dunnett's test).

Table 2. Mean overall ambulatory activity (count ± s.e.m.) for 1·5 h after the repeated administration of cocaine (10 mg kg^{-1}) in combination with SCH 23390 or YM-09151-2.

	Repeated administration					Cocaine
Drugs	1st	2nd	3rd	4th	5th	challenge
Cocaine alone	990 ± 89	1705 ± 286**	1924 ± 264**	2030 ± 221**	2028 ± 268**	1917 ± 345
Cocaine						
+SCH 23390 (0·01)	904 ± 103	1087 ± 181*,#	1428 ± 254**	1535 ± 201**,#	1543 ± 210**#	1877 ± 253
+SCH 23390 (0·03)	867 ± 118	870 ± 124##	1360 ± 182*,#	1353 ± 188*,##	1316 ± 141*,##	2710 ± 173#
+SCH 23390 (0·1)	176 ± 39	228 ± 43##	259 ± 38##	266 ± 52##	355 ± 58*,#	1944 ± 223
Cocaine						
+YM-09151-2 (0·01)	762 ± 93#	965 ± 124##	1335 ± 182*,#	1412 ± 166**,##	1571 ± 202**,#	2171 ± 312
+YM-09151-2 (0·03)	512 ± 88##	810 ± 86*,##	1188 ± 124**,##	1415 ± 163**,##	1515 ± 171**,#	3132 ± 319##
+YM-09151-2 (0·1)	214 ± 45##	332 ± 55##	534 ± 57**,##	578 ± 68**,##	625 ± 69**,##	2685 ± 179#
Saline	61 ± 15	58 ± 10	55 ± 11	65 ± 9	68 ± 12	977 ± 75##
No drugs						1016 ± 76

Figures in parentheses give the dose of the drug in mg kg^{-1}. n = 10 in each group. * and ** $P < 0·05$ and 0·01, respectively, vs the 1st administration within each group in the repeated administration schedule (Dunnett's test) and ## $P < 0·05$ and 0·01, respectively, vs the group administered cocaine alone (Dunnett's test).

progressive enhancement in its ambulation-increasing effect, i.e. induction of behavioural sensitization. The mean overall ambulatory activity count at the fifth administration was estimated to be about 2·3 times as high as that in the first administration. The activity counts after the combined administration of methamphetamine with SCH 23390 and with YM-09151-2 were lower than those after methamphetamine alone throughout the repeated administration. In particular, 0·03 mg kg^{-1} of both SCH 23390 and YM-09151-2 almost completely inhibited the effect of methamphetamine throughout the repeated administration.

Furthermore, mice receiving the repeated administration of methamphetamine in combination with SCH 23390 (0·03 mg kg^{-1}) and with YM-09151-2 (0·01 and 0·03 mg kg^{-1}) showed significantly lower sensitivity than mice treated with methamphetamine alone when challenged with a single dose of methamphetamine.

The combination of cocaine with SCH 23390 or YM-09151-2

As shown in Table 2, in the first administration (i.e. the administration to the drug-naive mice), both SCH 23390 and YM-09151-2 dose-dependently reduced the ambulation-increasing effect of cocaine. Comparison of individual mean values revealed that SCH 23390 (0·1 mg kg^{-1}) and YM-09151-2 (0·03 and 0·1 mg kg^{-1}) significantly reduced the ambulation-increasing effect of cocaine.

The repeated cocaine administration elicited a sensitization to its ambulation-increasing effect. The mean overall ambulatory activity count at the fifth administration was about twice that at the first administration. The activity counts after the combined administration of cocaine with SCH 23390 and with YM-09151-2 were dose-dependently decreased compared with those after cocaine alone throughout the repeated administration. However, a progressive enhancement of the effect was induced after the combined administration of cocaine even with the highest dose (0·1 mg kg^{-1}) of SCH 23390 and YM-09151-2.

Neither SCH 23390 nor YM-09151-2 could inhibit the cocaine sensitization, but induced an increased sensitivity to cocaine. Thus, mice receiving the combined administration of cocaine with SCH 23390 (0·01 mg kg^{-1}) and with YM-09151-2 (0·01 and 0·03 mg kg^{-1}) demonstrated significantly higher activity counts than those receiving cocaine alone.

Discussion

The development of methamphetamine sensitization induced by repeated administration of methamphetamine was inhibited when methamphetamine was combined with either SCH 23390 or YM-09151-2. Thus, in the challenge-administration of methamphetamine, which was carried out four days after the 5th administration, the mice given the combination of methamphetamine with SCH 23390 or with YM-09151-2 showed lower activity than those given methamphetamine alone. Almost the same suppressing effects on methamphetamine sensitization have been demonstrated with the combination of methamphetamine and antipsychotics such as the non-selective D_1 and D_2 antagonist, haloperidol (Kuribara et al 1986), and the selective D_2 antagonist, sulpiride (Asami et al 1987) in terms of ambulatory activity in mice. Ujike et al (1989) reported inhibitory actions of SCH 23390 and YM-09151-2 on the methamphetamine sensitization in rats. It has been postulated that antipsychotics decrease the unit dose of amphetamines (Creese 1983), and thereby inhibit their acute effects. Hirabayashi & Alam (1981) reported that the sensitization to the ambulation-increasing effect of methamphetamine in mice was more marked when the dose was 2 mg kg^{-1} than 1 mg kg^{-1}. In this respect, it appears that SCH 23390 and YM-09151-2 reduced the unit dose of methamphetamine, and thereby inhibited the methamphetamine sensitization.

Both SCH 23390 and YM-09151-2 reduced the ambulation-increasing effect of cocaine. However, neither SCH 23390 nor YM-09151-2 could completely inhibit the progressive enhancement of the effect in the repeated administration schedule, and both failed to inhibit the development of cocaine sensitization; several combinations of cocaine with SCH 23390 and YM-09151-2 produced a further enhancement of the cocaine sensitization. Such results clearly indicate that the cocaine sensitization is different from the methamphetamine sensitization in terms of the ambulatory activity in mice.

It has been suggested that amphetamines have actions on both facilitation of the dopamine-release and inhibition of dopamine-re-uptake, and cocaine has inhibitory action on dopamine-reuptake (Heikkila et al 1975; Fischman 1987). However, such properties would not explain the differential characteristics of methamphetamine and cocaine sensitization demonstrated in the present experiments. This is because both mechanisms result in an increase in the transmitter concentrations at the synapses of the dopaminergic neurons, and elicit similar stimulant actions on the central nervous system (Taylor & Ho 1977; McMillen 1983). It has been reported that cocaine, but not amphetamines, alter 5-HT-ergic mechanisms, blocking the synaptosomal uptake of tryptophan (Knapp & Mandell 1972) which results in a decrease in 5-HT synthesis (Mandell & Knapp 1977), and slows the turnover of 5-HT (Friedman et al 1975). Post et al (1976) suggested that the cocaine-induced psychotoxicity is more intimately related to an alteration in 5-HT metabolism than in catecholamine metabolism. Such mechanisms may account for differences between methamphetamine and cocaine in the interaction with dopamine antagonists, a view supported by the finding that the antagonistic actions of both SCH 23390 and YM-09151-2 on the stimulant effects of methamphetamine and cocaine were about three times more potent for methamphetamine than for cocaine, indicating different degrees of dopaminergic involvement.

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