Effects of YM-09151-2, a Potent and Selective Dopamine D2 Antagonist, on the Ambulation-Increasing Effect of Methamphetamine in Mice

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Abstract—The ambulation-increasing effect of methamphetamine (2 mg/kg, s.c.) was markedly reduced by YM-09151-2 at 0.01 mg/kg, s.c., in drug-naive mice. The development of reverse tolerance to the ambulation-increasing effect of methamphetamine was also inhibited almost completely when 0.01 mg/kg, s.c., of YM-09151-2 was administered concomitantly in each administration. However, YM-09151-2, at 0.01 mg/kg, was partially suppressed the effect of methamphetamine in mice that exhibited reverse tolerance to methamphetamine.

YM-09151-2, cis-N-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide, shows a potent and selective antagonistic action on dopamine D2 receptors (1), and its behavioral effects are similar to those of antipsychotic drugs (2, 3). The symptoms induced by amphetamines are partially similar to those of paranoidal schizophrenia (4–7).

Hence, the purposes of this experiment were to investigate whether YM-09151-2 was effective for inhibiting the reverse tolerance to methamphetamine by monitoring ambulatory activity in mice.

Experimental animals used were male mice of the dd strain (Institute of Experimental Animal Research, Gunma University School of Medicine). These mice were used at 10–12 weeks of age.

The apparatus for measuring ambulatory activity was a tilting-type ambulometer (AMB-10, O’Hara & Co.) (8).

The drugs used were YM-09151-2 (Yamanouchi Pharm. Co.) and methamphetamine HCl (Philopon®: Dainippon Pharm. Co.). YM-09151-2 was firstly dissolved in a very small amount of 0.1 N HCl, and then the solution was diluted by physiological saline, the vehicle. Methamphetamine was dissolved in physiological saline. The concentration of each drug solution was adjusted so that each volume injected was constant at 0.1 ml/10 g. The drugs were administered subcutaneously (s.c.).

Five groups of mice were given either methamphetamine (2 mg/kg) alone, YM-09151-2 (0.001, 0.003 or 0.01 mg/kg) plus methamphetamine (2 mg/kg), or physiological saline, 5 times at intervals of 3–4 days. These drugs were simultaneously administered, and the mouse’s ambulatory activity was observed for 3 hr after the drug (or vehicle) administration. Three to 4 days after the final (5th) administration, methamphetamine (2 mg/kg) was challenge-administered to all of these mice.

Another four groups of mice were first treated with the repeated 5 times administration of methamphetamine (2 mg/kg) at intervals of 3–4 days. Four days after the 5th administration, each group of mice were given 0.003 or 0.01 mg/kg YM-09151-2 in combination with 2 mg/kg methamphetamine or saline in combination with 2 mg/kg methamphetamine.

Figure 1 shows mean overall ambulatory activity counts for 3 hr after the repeated administration of methamphetamine alone, methamphetamine plus YM-09151-2 (0.001, 0.003 and 0.01 mg/kg), and saline alone. The repeated administration of methamphetamine elicited a progressive enhancement of its
ambulation-increasing effect. Thus, the mean overall ambulatory activity count in the 5th administration was estimated to be 2.3 times as high as the value in the 1st administration. Not only the ambulation-increasing effect of methamphetamine but also the reverse tolerance to it were suppressed in a dose-dependent manner when methamphetamine was administered in combination with YM-09151-2.

Figure 2 shows mean overall ambulatory activity counts after administration of methamphetamine to the drug-naive mice and to the mice that had received the repeated administration of methamphetamine alone or combination of methamphetamine plus YM-09151-2 (0.001, 0.003 and 0.01 mg/kg). The mice that had received the combination of methamphetamine plus YM-09151-2 (0.01 mg/kg) showed almost the same activity counts in the challenge administration of methamphetamine as those of the drug-naive mice.

The ambulation-increasing effect of methamphetamine was dose-dependently suppressed by YM-09151-2 even in the mice that exhibited the reverse tolerance to methamphetamine. However, YM-09151-2 (0.01 mg/kg) failed to completely inhibit the ambulation-increasing effect of methamphetamine in the methamphetamine-experienced mice (mean activity counts=2038±279), although this dose of YM-09151-2 completely suppressed the effect of methamphetamine in the drug-naive mice (mean activity counts=304±54).

The present experiment demonstrated the neuroleptic property of YM-09151-2, suppressing the ambulation-increasing effect of methamphetamine. YM-09151-2 was also effective for inhibiting the development of reverse tolerance to methamphetamine when the two drugs were administered in combination. Almost the same results have been observed after the combined administration of haloperidol plus methamphetamine (9) and chlorpromazine plus d-amphetamine (10). The comparison of the dose-effect relationships revealed that the anti-amphetamine effect of YM-09151-2 is 40 and 400 times as potent as that of haloperidol or chlorproma-
It has been reported that the inhibitory effect of YM-09151-2 on the \( ^3\)H-spiperon binding to the dopamine D\(_2\) receptors is 10 and 70 times, respectively, as strong as those of haloperidol and chlorpromazine in vitro (1), indicating that YM-09151-2 can readily pass through the blood-brain barrier after its systemic administration and shows a potent antipsychotic action.

Although YM-09151-2, at 0.01 mg/kg, not only inhibited almost completely the ambulation-increasing effect of methamphetamine in the drug-naive mice, but also suppressed the development of reverse tolerance to the effect of methamphetamine. However, the same dose failed to completely inhibit the ambulation-increasing effect of methamphetamine in mice that already exhibited reverse tolerance. Koshiya and Usuda (11) reported a similar result by means of methamphetamine-induced stereotyped behavior in rats. These findings support the hypothesis that a functional change of dopamine D\(_2\) receptors, if it is induced, is not a principal factor in the development of the reverse tolerance to methamphetamine.

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