SCH 23390 Equivalently, but YM-09151-2 Differentially Reduces the Stimulant Effects of Methamphetamine, MK-801 and Ketamine: Assessment by Discrete Shuttle Avoidance 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

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ABSTRACT—The inhibitory actions of the selective dopamine D1- and D2-antagonists SCH 23390 and YM-09151-2, respectively, on the mouse’s discrete shuttle avoidance were almost equipotent at doses ranging from 0.01 – 0.1 mg/kg. SCH 23390 reduced the stimulant action of methamphetamine (0.5 mg/kg), MK-801 (0.1 mg/kg) and ketamine (10 mg/kg) with a similar potency. YM-09151-2 also antagonized the actions of these drugs, with the following order of effectiveness: ketamine > MK-801 > methamphetamine. The present results indicate that methamphetamine, MK-801 and ketamine have different characteristics of CNS stimulant action through dopamine D2-receptors.

Keywords: Dopamine D1- and D2-antagonists, Stimulant, Discrete shuttle avoidance

The non-competitive NMDA antagonist MK-801 (dizocilpine) and the dissociative anesthetic ketamine have behavioral stimulant actions: they increase the ambulatory (locomotor) activity at a comparatively lower dose, and they induce stereotypy at a higher dose in rodents (1–4), producing an ipsilateral turning in rats having 6-OHDA-induced unilateral nigrostriatal lesion (5, 6). These findings indicate that both MK-801 and ketamine indirectly stimulate the central dopaminergic systems. Neurochemical investigations have also demonstrated that MK-801 or ketamine causes an increase in the dopamine release from presynaptic dopaminergic neurons (6, 7); this action is similar to that of methamphetamine (8). However, there are some characteristic differences among these drugs. The ambulation-increasing effect of methamphetamine and ketamine can be inhibited by α-methyl-p-tyrosine, whereas that of MK-801 is inhibited by reserpine (3, 4, 9).

In this study, we further evaluated the characteristics of the CNS stimulant effects of methamphetamine, MK-801 and ketamine through combined administration with the selective dopamine D1- and D2-antagonists SCH 23390 (10, 11) and YM-09151-2 (12), respectively, by means of discrete shuttle avoidance in mice. Shuttle avoidance has been empirically considered to be convenient for detecting both the behavioral stimulant and depressant actions of drugs (13).

Male mice of the ddY strain (Japan Laboratory Animals, Tokyo) were used from the age of 8 weeks. Throughout the experiment, these mice were kept in a controlled room (12-hr light-dark schedule with a light period of 6:00–18:00, temperature of 22 ± 1 °C, and relative humidity of 50 ± 2%) with free access to food and tap water.

The drugs used were methamphetamine HCl (Phippon, Dainippon Pharm., Osaka), MK-801 hydromaleate (dizocilpine, Merck/Banyu, Tokyo), ketamine HCl (Ketalar, Sankyo, Tokyo), SCH 23390 (Research Biochem., Natick, MA, USA), and YM-09151-2 (Yamanouchi Pharm., Tokyo). YM-09151-2 was first dissolved in a small amount of 1 N HCl solution, and then the solution was diluted with physiological saline. The other drugs were dissolved or diluted with the saline. The drugs were administered s.c. at a fixed volume of 0.1 ml/10 g body weight regardless of the doses.

The present experiment was run with the shuttle box, behavior-controlling and data-recording units (GT-8450, De CARES GT-M5 and TIDP-10, respectively; O’Hara & Co., Tokyo). The temporal parameters of the discrete avoidance schedule were an intertrial interval of 25 sec and a warning period (indicated by an 800-Hz tone signal) of 5 sec. An electric current (100 V, 0.3 mA, 50 Hz AC) was presented for 0.3 sec to the mouse’s feet through the floor grid of the chamber when the mouse failed to make an avoidance response (shuttle) during the warning
period. The indices of the avoidance behavior were the response rate (frequency of shuttles) and the % avoidance (avoidance responses/avoidance trials).

Methamphetamine, MK-801 and ketamine were administered immediately before the avoidance session of 30 min, in which 60 avoidance trials were held at intervals of 30 sec. The animals were treated with SCH 23390 or YM-09151-2 20 min prior to the avoidance session. The drug-testing sessions were run at intervals of 3–4 days, and the days before saline was administered as the control and/or baseline sessions. Three groups of 10 mice each were trained and used for the experiments as follows: the 1st group was used to evaluate the effects of the single administration of SCH 23390 and YM-09151-2 and the other groups were used to test the effects of combining SCH 23390 (2nd group) or YM-09151-2 (3rd group) with methamphetamine, MK-801 and ketamine. The orders of evaluation of methamphetamine, MK-801 and ketamine were randomized among the mice. However, in each drug evaluation, the doses of SCH 23390 and YM-09151-2 administered were changed from lower to higher in the 5 mice and changed in the reverse order in the other 5 mice. All the experiments were held between 9:00–14:00.

The 30-min overall response rate and the % avoidance were first analyzed by ANOVA, followed by the individual comparisons by Dunnett's test. When the P value was equal to or less than 0.05, the two values were considered to be significantly different.

As shown in Fig. 1, SCH 23390 and YM-09151-2 inhibited the avoidance behavior. Thus, both drugs significantly decreased the response rate at 0.01 mg/kg and the % avoidance at 0.03 mg/kg. There was no significant difference in the avoidance-inhibitory actions of SCH 23390 and YM-09151-2.

As shown in Fig. 2, methamphetamine (0.5 mg/kg), MK-801 (0.1 mg/kg) and ketamine (10 mg/kg) almost equivalently enhanced the avoidance behavior; increasing the response rate to 2.2–2.5 times as high as those of the corresponding saline-administered baseline level. SCH 23390 inhibited the effects of methamphetamine, MK-801 and ketamine with almost the same dose-effect relationships for both the response rate and the % avoidance (left panel). YM-09151-2 also antagonized the actions of these 3 drugs, with the following decreasing order of effectiveness: ketamine > MK-801 > methamphetamine.

The present experiment confirmed the neuroleptic action of SCH 23390 and YM-09151-2: inhibiting the discrete avoidance response and showing anti-amphetamine action. The avoidance-inhibiting actions of both SCH 23390 and YM-09151-2 were completely reversible, and the pre-drug baseline avoidance response was re-established by the day after drug administration. Such results indicate that the avoidance-inhibition is not produced through learning and memory processes.

Although it has been considered that the neuroleptic activities of drugs are correlated with the blockade action on the dopamine D2-receptors (14), the present results indicate that the blockade of either D1- or D2-receptors is sufficient for exhibiting the neuroleptic actions. Similar results have been also demonstrated elsewhere (10, 11). Furthermore, the dose-effect relationships obtained in this experiment indicate that the avoidance-suppressing actions are almost equipotent between SCH 23390 and YM-09151-2 when they are administered singly.

On the other hand, the response-increasing effects of methamphetamine (0.5 mg/kg), MK-801 (0.1 mg/kg) and ketamine (10 mg/kg) were almost the same, and these effects could be antagonized dose-dependently by SCH 23390 and YM-09151-2. The antagonistic actions of SCH 23390 were almost identical among methamphetamine, MK-801 and ketamine, suggesting that there is no remarkable difference in the actions of these drugs through dopamine D1-receptor systems. However, taking into account the results of the present study, it is considered that there are characteristic differences in the CNS stimulant actions of the 3 drugs in terms of their effect on the dopamine D2-
receptor systems. Thus, the dose-effect relationships revealed that, although the potencies of the avoidance-suppressing effect as well as the antagonistic actions for ketamine were almost the same between SCH 23390 and YM-09151-2, the antagonistic actions of YM-09151-2 against methamphetamine and MK-801 were about 1/10 and 1/3, respectively, as high as that for ketamine. We have reported that the stimulant effects of comparatively lower doses of MK-801 and ketamine are selectively reduced by reserpine and α-methyl-p-tyrosine, respectively (3, 4), indicating that the properties of ketamine, but not MK-801, are very similar to those of methamphetamine (8). However, such differences in properties are inadequate for explaining the differential dose-effect relationships for the interactions of these 3 drugs with YM-09151-2. Methamphetamine, but not MK-801 and ketamine, has an inhibitory action on dopamine reuptake at presynaptic terminals (8), whereas MK-801 and ketamine, but not methamphetamine, possess non-competitive NMDA antagonistic action as well as agonistic action on sigma-receptors (1, 9).

Moreover, the methamphetamine-induced change in the monoamine synthesis at presynaptic neurons (15) may be differentially responsible for the actions of dopamine D1- and D2-antagonists (2, 10). Such differences may result in YM-09151-2 having a weaker antagonistic action than SCH 23390 on the stimulant effect of methamphetamine.

REFERENCES


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