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Effects of Chronic Methamphetamine on SCH23390- or Haloperidol-Induced Catalepsy, and Effects of Coadministration of SCH23390 or Haloperidol in Mice

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MIZUKI, Y., I. USHIJIMA AND M. YAMADA. *Effects of chronic methamphetamine on SCH23390- or haloperidol-induced catalepsy, and effects of coadministration of SCH23390 or haloperidol in mice.* PHARMACOL BIOCHEM BEHAV 53(2) 437–440, 1996.—The influence of chronic treatment of mice with methamphetamine, an indirect dopamine agonist, on the cataleptic effects of R-(+)-chloro-2,3,4,5,-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7ol hydrochloride (SCH23390), a D_1 receptor agonist, or haloperidol, a mainly D_2 antagonist, was investigated. Once every other day treatment with 3 mg/kg SC methamphetamine for 15 days resulted in an increase in the catalepsy produced by haloperidol (0.3 mg/kg IP) (haloperidol catalepsy), but in a decrease in the catalepsy produced by SCH23390 (0.3 mg/kg IP) (SCH23390 catalepsy), 24 h and 7 days after withdrawal of methamphetamine. These effects of chronic methamphetamine were antagonized by coadministration of either SCH23390 (0.5 mg/kg SC) or haloperidol (1.0 mg/kg SC). These results suggest that the decreased responsiveness to SCH23390 in chronic methamphetamine-pretreated mice results from a supersensitivity of D_1 receptors, and that the increased responsiveness to haloperidol catalepsy results from a subsensitivity of D_2 receptors. The attenuated response to SCH23390 may be interpreted as an example of sensitization to methamphetamine, and the enhanced haloperidol response as an example of tolerance to methamphetamine, based on the development of supersensitivity and subsensitivity of D_1 and D_2 receptors, respectively, after chronic methamphetamine administration. Furthermore, it is suggested that coadministration of either SCH23390 or haloperidol could prevent the development of D_1 receptor supersensitivity and D_2 receptor subsensitivity induced by chronic methamphetamine.

Chronic methamphetamine SCH23390 Haloperidol Catalepsy Mice

CHRONIC exposure to a drug frequently results in the development of tolerance, that is, a decrease in responsiveness to a drug. In contrast to tolerance, as a result of chronic treatment with dopamine agonists, is the phenomenon of reverse tolerance, which is an increase in responsiveness of certain behaviors. Central locomotor stimulants, such as cocaine and methamphetamine, have been shown to produce sensitization or reverse tolerance to behavioral responses such as hyperlocomotion (11,19) and stereotypy (10,16). These supersensitive responses in animals have been considered as analogous to the methamphetamine-induced psychosis and schzophrenia-like symptoms in humans (4,17,18). However, these drugs also exhibit the phenomenon of tolerance to other behavioral effects such as in the convulsive threshold lowering of amphetamine (5,16). All of these behaviors are thought to be mediated via the dopamine system.

We have observed that after chronic treatment with D_1 antagonist SCH23390, mice exhibited an increased catalepsy to subsequent SCH23390 administration, which was interpreted as resulting from D_1 receptor subsensitivity, whereas after chronic D_2 antagonist haloperidol, the opposite effect (D_2 receptor supersensitivity) was seen (23). The importance in the link between dopamine neurotransmission in CNS and psychotic symptomatology is the fact that most neuroleptic (anti-

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psychotic) drugs act as postsynaptic dopamine receptor blockers, and this effect correlates with their therapeutic potency (15). One of the behavioral tests for neuroleptic activity is to measure the ability of a drug to induce a cataleptic state in rodents (3,8). The purpose of this study was to investigate the effects of chronic treatment with methamphetamine on SCH23390- or haloperidol-induced catalepsy, and then how the effects of chronic methamphetamine were altered by concomitant administration of SCH23390 or haloperidol.

METHOD

Animals

Male ddY mice (6- or 7-week-old, 20–25 g) were obtained from Kyudo Animal Laboratory (Saga, Japan) and maintained in an animal room at an environmental temperature of 23 ± 1°C, with a 12 L : 12 D cycle (0700–1900 h). Commercial food (MF, Oriental Yeast Ltd.) and tap water were available ad lib except during the time of the experiments. All experiments were performed by using 8- or 9-week-old mice weighing 30–40 g.

Measurement of Catalepsy

Catalepsy responses were measured using the bar-suspension method by placing mice individually on a plastic board (25 × 35 cm) with a horizontal wire bar (3 mm in diameter, sealed with vinyl) suspended 5 cm above the floor. The animals' front paws were placed gently on the bar, and the time taken for the mouse to remove both paws from the bar was recorded. A preset cutoff time of 10 min was used. We observed cataleptic responses 15, 30, 60, and 120 min after SCH23390 (0.3 mg/kg IP) or haloperidol (0.3 mg/kg IP). For simplification, the data were scored according to the following scale: 0 = 0–29 s; 1 = 30–59 s; 2 = 60–119 s; 3 = 120–179 s; 4 = 180–239 s; 5 = 240–299 s; 6 = 300–359 s; 7 = 360–419 s; 8 = 420–479 s; 9 = 480–539 s; and 10 = 540–599 s.

Administration of Drugs

Mice were divided into the following treatment groups: saline (5 ml/kg SC); methamphetamine (3 mg/kg SC); SCH23390 (0.5 mg/kg SC) + methamphetamine (3 mg/kg SC); and haloperidol (1 mg/kg SC) + methamphetamine (3 mg/kg SC). These drugs were administered to mice once every other day at 1000 for 15 days. To observe the cataleptic effects, we administered SCH23390 (0.3 mg/kg IP) or haloperidol (0.3 mg/kg IP) 24 h and 7 days after the last injection. We selected the challenge dose of SCH23390 (0.3 mg/kg) or haloperidol (0.3 mg/kg) from a previous report in which were observed the dose-response effects of these drugs, that is, the increasing and decreasing effects of catalepsy (23).

Drugs

Drugs used were methamphetamine hydrochloride (Dainippon, Osaka, Japan), R-(+)-SCH23390 hydrochloride (RBI, Natick, MA) and haloperidol (Dainippon, Osaka, Japan).

Statistics

The data are expressed as mean ± SEM. Each group consisted of a 10 or 11 animals. Catalepsy score data were analyzed nonparametrically utilizing a statistical analysis software. Statistical tests were the Kruskal-Wallis test followed by the Mann-Whitney *U*-test for individual comparisons if the Kruskal-Wallis test indicated a significant difference. The level of significance chosen was $p < 0.05$.

RESULTS

Time Course of Cataleptic Responses to SCH23390 and Haloperidol

In 15-day saline (chronic saline)-treated mice, SCH23390 (0.3 mg/kg IP) evoked cataleptic responses of rapid onset and short duration with a maximal effect at 15–30 min after injection. The cataleptic effect of haloperidol (0.3 mg/kg IP) appeared slowly and was more prolonged as compared to SCH23390 (Fig. 1, open circles in A and C).

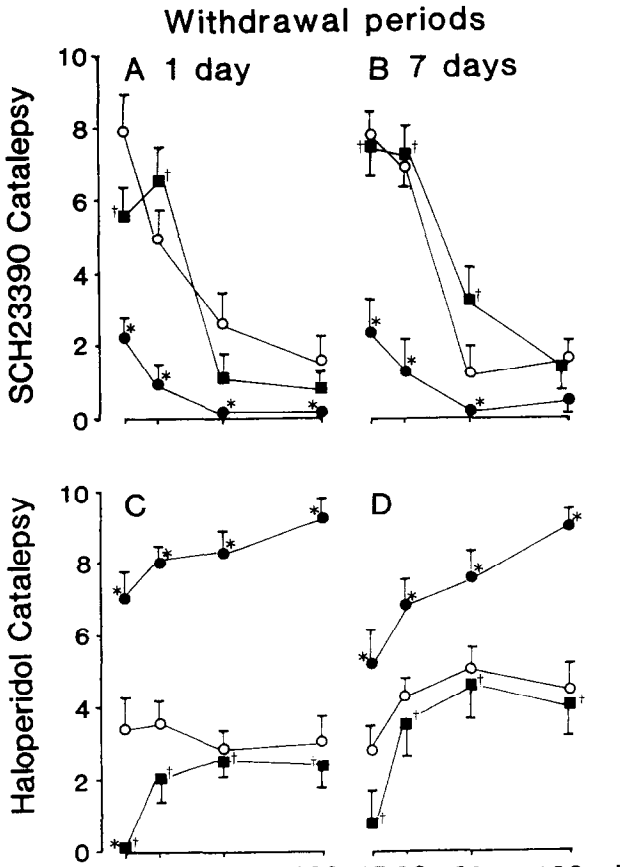

FIG. 1. Effects of chronic methamphetamine on cataleptic responses induced by dopamine antagonists, and effects of coadministration of SCH23390 in mice. Groups of mice received saline (5 ml/kg SC) (open circles), methamphetamine (3 mg/kg SC) (closed circles), or methamphetamine + SCH23390 (0.5 mg/kg SC) (closed squares) once every other day for 15 days. They were then challenged with SCH23390 (0.3 mg/kg IP) or haloperidol (0.3 mg/kg IP) 1 and 7 days after the last pretreatment injection. Panels A and B represent the catalepsy scores to the challenge dose of SCH23390 and panels C and D to haloperidol. *,†$p < 0.002$ as compared to saline (*) and to methamphetamine (†).

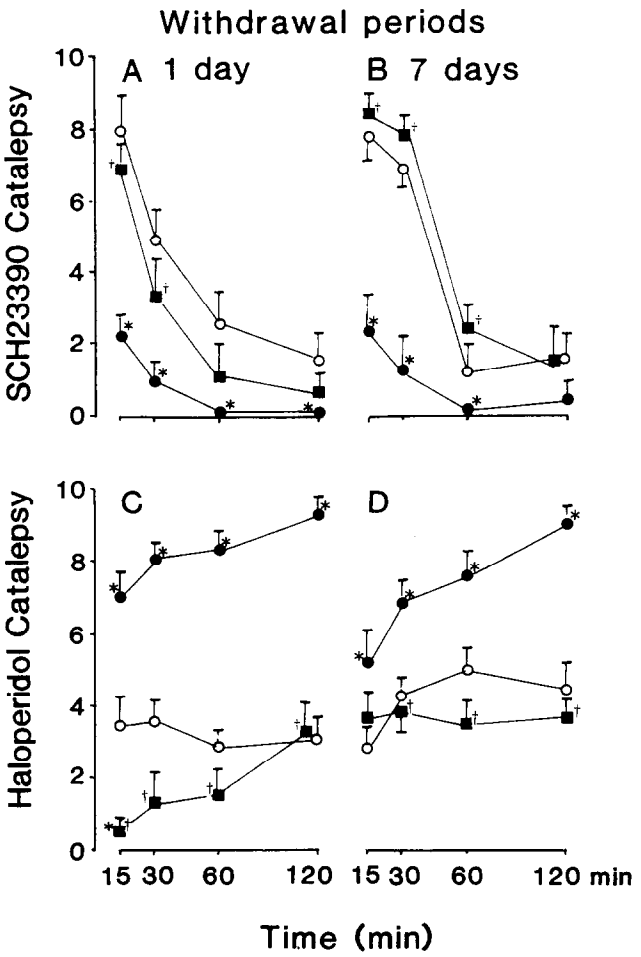

FIG. 2. Reversible effects of chronic methamphetamine-induced changes in cataleptic responses by coadministration of haloperidol. Mice received methamphetamine + haloperidol (1 mg/kg SC) (closed squares) once every other day for 15 days. Further explanation as in Fig. 1.

Time Course of Cataleptic Response to SCH23390 and Haloperidol in Chronic Methamphetamine- and Methamphetamine + Dopamine Antagonist-Pretreated Mice

On days 1 and 7 after chronic methamphetamine pretreatment (3 mg/kg SC for 15 days) a challenge dose of SCH23390 produced a subnormal cataleptic response (Fig. 1A and B, closed circles), while a challenge dose of haloperidol produced a supernormal response (Fig. 2C and D, closed circles).

These inhibitory and stimulatory effects of chronic methamphetamine (3 mg/kg SC) on SCH23390 and haloperidol cataleptic responses, respectively, were reversed by coadministration of either SCH23390 (0.5 mg/kg SC) (Fig. 1, closed squares) or haloperidol (1 mg/kg SC) (Fig. 2, closed squares).

DISCUSSION

The results of this study have demonstrated that chronic treatment of mice with methamphetamine resulted in an increased sensitivity to the cataleptic actions of haloperidol and a decreased sensitivity to those of SCH23390. These effects persisted more than 7 days after the last injection of methamphetamine. Our finding of an altered response to haloperidol is consistent with previous reports (13). The decrease in the cataleptic response to SCH23390 after chronic exposure to methamphetamine could be interpreted as a development of supersensitivity of D_1 receptors (reverse tolerance to methamphetamine), whereas the increase in haloperidol catalepsy as a subsensitivity of D_2 receptors (tolerance to methamphetamine). If that were the case it would indicate that the D_1 receptor may be mainly involved in psychostimulant-induced sensitization, which in man is manifested as methamphetamine-induced psychosis and schizophrenia-like symptoms (4,17,18). It has been reported that chronic D_2 dopamine receptor stimulation by D_2 agonists such as LY171555 (1), bromocriptine (6), and lisuride (2) produces behavioral subsensitivity, whereas chronic D_1 agonist SK&F38393 administration produces supersensitivity (1). The behavioral sensitization induced by chronic exposure to an indirect dopamine agonist such as methamphetamine, may involve both D_1 receptor supersensitivity and D_2 receptor subsensitivity. Furthermore, chronic dopamine precursor, such as L-dopa, enhanced dopamine-sensitive adenyl cyclase activity (14), suggesting that the sensitivity of the dopamine D_1 receptor coupled cyclase might be increased.

Previous reports (9,22) have shown that methamphetamine-induced sensitization can be blocked by coadministration of haloperidol or SCH23390. In addition, the treatment with D_1 and D_2 receptor antagonists also prevented the neurochemical changes of enhanced dopamine release from the sensitized striatum (7). In this study, we found that the decreased SCH23390 catalepsy (D_1 receptor supersensitivity) and the increased haloperidol catalepsy (D_2 receptor subsensitivity) induced by chronic methamphetamine were antagonized by coadministration of either SCH23390 or haloperidol. These results were somewhat surprising because we had expected that the coadministration of haloperidol would result in a decreased SCH23390 catalepsy and an unaffected haloperidol catalepsy, and SCH23390 would increase haloperidol catalepsy and leave unaffected SCH23390 catalepsy. That the cataleptic effects induced by SCH23390 and haloperidol can be suppressed by D_2 receptor agonists has been reported (12). However, we have found that the D_2, but not D_1, receptor agonist inhibited haloperidol catalepsy (unpublished observation). These results suggest that SCH23390 catalepsy may be indirectly mediated by D_2 receptor activity (12), but haloperidol catalepsy may not involve D_1 receptor activity (23). Thus, coadministration of haloperidol could be expected to inhibit both D_1 receptor stimulation (supersensitivity) and D_2 receptor inhibition (subsensitivity) induced by chronic methamphetamine. On the other hand, the coadministration of SCH23390 as well as haloperidol blocked D_2 receptor inhibition (subsensitivity) induced by chronic methamphetamine, despite the fact that by itself did not have an effect on haloperidol catalepsy. Accordingly, these results suggest that the stimulatory effects of D_2 receptors by a single administration of methamphetamine may be mediated by mainly an indirect stimulation of D_2 receptor function via its D_1 receptor stimulating action. Both SCH23390 and haloperidol seem to normalize abnormal symptoms induced by chronic methamphetamine. Behavioral sensitization by amphetamine was attenuated by concomitant microinjections of SCH23390 into the ventral tegmental area and the substantia nigra reticulata (20). These results indicate that stimulation of ventral tegmental and nigral D_1 receptors by amphetamine, probably via excessively released dopamine

from the dendrites, is necessary for the development of behavioral sensitization. Recently, autoradiographic studies have revealed the long-lasting increase in dopamine D_1 receptors in the lateral part of the substantia nigra par reticulata after chronic methamphetamine administration, suggesting that a lasting increase in the nigral D_1 receptors may be associated with the biological changes underlying methamphetamine induced behavioral sensitization (21). Therefore, chronic methamphetamine-induced sensitization (decrease of SCH23390 catalepsy) and subsensitization (increase of haloperidol catalepsy) may occur via dopamine D_1 receptor function.

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