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Alteration of cataleptic responses induced by dopamine receptor antagonists after chronic cocaine administration in mice

Itsuko Ushijima *, Yasushi Mizuki, Michio Yamada

Department of Neuropsychiatry, School of Medicine, Yamaguchi University, 1144 Kogushi, Ube, Yamaguchi 755, Japan

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Abstract

The influence of chronic treatment of mice with cocaine, an indirect dopamine receptor agonist, on the cataleptic effects of *R*-(+)-chloro-2,3,4,5,-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7ol hydrochloride (SCH23390), a dopamine D_1 receptor antagonist, or haloperidol, mainly a dopamine D_2 receptor antagonist, was investigated. Mice were given cocaine (10 mg/kg s.c.) once every other day for 7 (4 injections), 15 (8 injections) or 21 (11 injections) days. The cataleptic effects of SCH23390 (0.3 mg/kg i.p.) were significantly reduced when it was given 1–7 days after the last dose of a 7- or 15-day pretreatment course of cocaine. When SCH23390 was given 14–21 days after the cocaine the cataleptic effect was increased in the 15-day, but not the 7-day, cocaine-pretreated mice. However, after a 21-day treatment with cocaine, a challenge dose of SCH23390 given 1–3 days thereafter produced a decreased cataleptic response, but an increased response after 7–21 days. The cataleptic effects of haloperidol (0.3 mg/kg i.p.) were reduced when it was given 1–7 days after the last dose of a 7-day pretreatment, but increased 1–3 days after that of a 15-day pretreatment with cocaine (10 mg/kg s.c.). The pretreatment with cocaine for 21 days did not affect the haloperidol catalepsy during a 1- to 3-day withdrawal period. However, haloperidol catalepsy was decreased only 7 days, then reversed 14 days and gradually increased 21 days after the last injection of a 15- or 21-day pretreatment course of cocaine. These results suggest that chronic treatment with the indirect dopamine receptor agonist, cocaine, caused supersensitivity of dopamine D_1 receptors (a decrease in SCH23390 catalepsy) during the early withdrawal period and subsensitivity (an increase in SCH23390 catalepsy) after a longer period of withdrawal. It was apparent that the longer the period and the higher the dose of pretreatment with cocaine, the less were the alterations in initial responses and the greater were the alterations in subsequent responses to the dopamine D_1 receptor antagonists.

Keywords: Cocaine; SCH23390; Haloperidol; Catalepsy; Supersensitivity; Subsensitivity; (Mouse)

1. Introduction

Chronic treatment with psychomotor stimulants such as methamphetamine and cocaine may produce either sensitization or tolerance, depending upon the behavioral or physiological endpoint (Johanson and Fischman, 1989). The behavioral sensitization is presumed to be the result of increasing release, decreasing reuptake and/or inhibiting metabolism of catecholamines and indole amine in mesolimbic and striatal terminal fields (Weiner, 1985). The psychotropic effects of cocaine are usually attributed to its ability to block the reuptake of dopamine into mesocortical or mesolimbic neurons, rather than to its ability to block the reuptake of serotonin and norepinephrine (Galloway, 1988). Higher doses of cocaine also induce hyperlocomotor activity and stereotyped behaviors in animals. The predominant cocaine-induced behaviors shift from those of locomotor hyperactivity to stereotyped behaviors with increasing dose or number of injections (Post et al., 1987). However, these drugs also lead to tolerance to other behavioral effects such as the convulsive threshold-lowering of amphetamine (Post et al., 1987), the increasing effect of chronic amphetamine on haloperidol-induced catalepsy (Muller and Seeman, 1979) and the tolerance to suppressive effects of cocaine on milk drinking (Bowen et al., 1993). All of these behaviors are thought to be mediated via the dopaminergic system. It is possible that both supersensitivity and subsensitivity to dopaminergic drugs may be

* Corresponding author.

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the result of alterations of different dopamine receptors (dopamine D_1 and D_2 receptors) during long-term cocaine treatment. Catalepsy and stereotyped behaviors are generally believed to be pharmacologically opposed behavioral effects which result from blockade and stimulation of dopamine receptors, respectively. Thus, the purpose of this study was to investigate the effects of chronic treatment with cocaine, an indirect dopamine agonist, followed by various withdrawal periods on catalepsy induced by SCH23390, a dopamine D_1 receptor antagonist, or haloperidol, a mainly dopamine D_2 receptor antagonist.

2. Materials and methods

2.1. Animals

Healthy male *ddY* albino mice (4–6 weeks, 20–32 g), purchased from Kyudo Animal Laboratory (Saga, Japan), were allowed free access to food and water. The mice were housed and all trials were carried out at an environmental temperature of 23 ± 1°C, with a 12-h light-dark cycle (light on 7:00 a.m.–light off 7:00 p.m.). We used 7-week-old mice for a 7-day pretreatment, 6-week-old mice for a 15-day pretreatment and 5-week-old mice for a 21-day pretreatment at the start of the study. All experiments were thus performed with 8-week-old mice weighing 35–40 g.

2.2. Measurement of catalepsy

Cataleptic responses were measured by means of the bar method by placing mice (8 weeks, 35–40 g) individually on a plastic board (25 × 35 cm) with a horizontal wire bar (diameter 3 mm, sealed with vinyl) suspended 5 cm above the floor. We used 10 devices with 10 stopwatches to ensure methodical observation. The observers were blinded with respect to treatment. The animal's front paws were placed gently on the bar, and the time taken for the mouse to remove both paws from the bar was recorded. To study the timing of the catalepsy, we tested cataleptic responses 15, 30, 60 and 120 min after SCH23390 (0.3 mg/kg i.p.) or haloperidol (0.3 mg/kg i.p.). To examine the dose-related effects of catalepsy, we observed cataleptic responses 15 min after challenge dose of SCH23390 (0.1–1.0 mg/kg i.p.) and 30 min after that of haloperidol (0.1–1.0 mg/kg i.p.) for 15 min. A preset cut-off time of 15 min was used. 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; 10: 540–599 s; 11: 600–659 s; 12: 660–719 s; 13: 720–779 s; 14: 780–839 s; 15: greater than 840 s.

2.3. Administration of drugs

Mice (4–6 weeks, 20–32 g) received cocaine (10 mg/kg s.c.) or saline (5 ml/kg s.c.) once every other day for 7 (4 injections), 15 (8 injections) or 21 (11 injections) days. The injections followed by behavioral observation were carried out every day at 10:00 a.m. for saline and at 11:00 a.m. for cocaine. To observe the cataleptic effects we administered SCH23390 (0.3 mg/kg i.p.) or haloperidol (0.3 mg/kg i.p.) at 1.5-min intervals 1,3,7,14 or 21 days after the last injection of the pretreatment regimen. We used the same mice on day 1 and on day 14, or on day 3 and day 21. To observe the dose-related effect of catalepsy, we administered SCH23390 (0.1–1.0 mg/kg i.p.) or haloperidol (0.1–1.0 mg/kg i.p) 1 day and 14 days after the last dose of the 15-day pretreatment with cocaine (5–20 mg/kg s.c.) (8 injections).

2.4. Drugs

The drugs used were cocaine hydrochloride (Takeda, Osaka, Japan), *R*-(+)-chloro-2,3,4,5,-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7ol hydrochloride (SCH23390: RBI, Natric, MA, USA) and haloperidol hydrochloride (Dainippon, Osaka, Japan). All drugs were dissolved in saline and an equal volume of vehicle (5 ml/kg) was injected.

2.5. Statistics

The data are expressed as means ± S.E.M. Each group consisted of 10 animals. The significance of differences between data for saline- and cocaine-injected groups was analyzed using Mann-Whitney *U*-tests. A value of $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Cataleptic responses to SCH23390 or haloperidol

In 7-, 15- or 21-day saline (once every other day)-treated mice, SCH23390 (0.3 mg/kg i.p.) evoked cataleptic responses with rapid start and short duration with a maximal effect at 15–30 min after injection. The cataleptic effect of haloperidol (0.3 mg/kg i.p.) appeared slowly and was more prolonged than that of SCH23390 (open circles in Fig. 1 and Fig. 2).

3.2. Dependence on duration of cocaine exposure and period of withdrawal on the cataleptic responses to challenge doses of SCH23390

On days 1–7 after chronic cocaine (10 mg/kg s.c.) pretreatment for 7 (4 injections) or on days 1–3 for 15

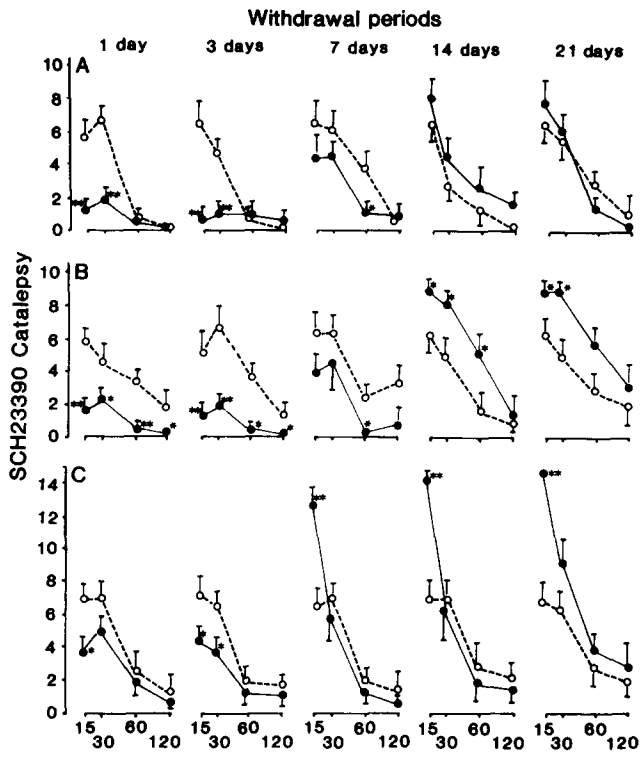

Fig. 1. Alteration of cataleptic responses to a challenge dose of SCH23390 in mice 1–21 days after chronic treatment with cocaine. Groups of mice received saline (5 ml/kg s.c.) or cocaine (10 mg/kg s.c.) once every other day for 7 (A), 15 (B) and 21 (C) days. They were then challenged with SCH23390 (0.3 mg/kg i.p.) 1, 3, 7, 14 and 21 days after the last pretreatment injection. Saline (open circles) and cocaine (closed circles), ** $P < 0.002$, * $P < 0.05$ as compared to saline-injected group

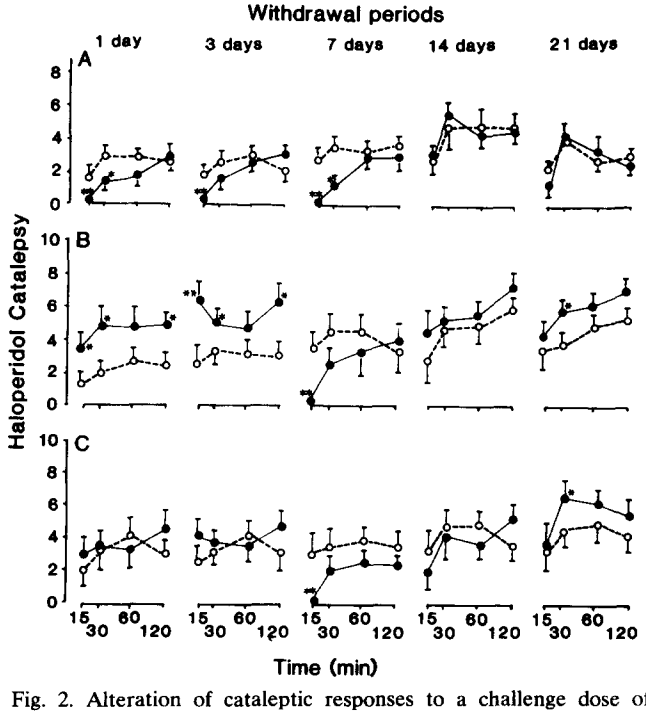

Fig. 2. Alteration of cataleptic responses to a challenge dose of haloperidol in mice 1–21 days after chronic treatment with cocaine. Further explanations as in Fig. 1.

(8 injections) days, a challenge dose of SCH23390 (0.3 mg/kg i.p.) produced subnormal cataleptic responses (Fig. 1A and B) ($P < 0.002$: 15–60 min after a challenge dose of SCH23390). An increase of SCH23390 catalepsy ($P < 0.05$: 15, 30 or 60 min after challenge dose) was seen 14–21 days after the last dose of a 15-day pretreatment with cocaine (10 mg/kg s.c.) (Fig. 1B). However, in animals exposed to 21-day cocaine pretreatment (11 injections), a challenge dose of SCH23390 produced, during days 1–3 after cocaine, an attenuated cataleptic response ($P < 0.05$), which was converted during days 7–21 into an enhanced cataleptic response. This enhanced cataleptic response ($P <$ 0.05: greater than 15 min) was seen only at 15 min, but was quickly reversed 30, 60 and 120 min after a challenge dose of SCH23390 (0.3 mg/kg i.p.) (Fig. 1C).

3.3. Effects of duration of cocaine exposure and period of withdrawal on the cataleptic responses to challenge doses of haloperidol

The cataleptic effects of haloperidol (0.3 mg/kg i.p.) were decreased when it was given 1 and 7 days and was not affected 14–21 days after the last dose of a 7-day cocaine pretreatment (Fig. 2A). However, haloperidol catalepsy was increased 1–3 days after the last dose of a 15-day cocaine pretreatment (Fig. 2B), but was not affected 1–3 days after that of a 21-day pretreatment course with cocaine (Fig. 2C). The intensity of haloperidol-induced catalepsy was decreased 7 days ($P < 0.002$: only 15 min after haloperidol), gradually reversed 15 days, and increased at 21 days ($P < 0.05$: 30 min after haloperidol) after both 15- and 21-day cocaine pretreatment (Fig. 2B and C).

3.4. Dose-related effects of catalepsy in response to SCH23390 and haloperidol, and cocaine

As shown in Fig. 3 (A, B, C and D), the cataleptic responses to the challenge dose of SCH23390 (0.1–1.0 mg/kg i.p.) or haloperidol (0.1–1.0 mg/kg i.p.) exhibited dose dependence after any chronic pretreatment dose with cocaine for 15 days (8 injections).

The cataleptic effects of SCH23390 (0.1–1.0 mg/kg i.p.) were significantly decreased when it was given 1 day after the last dose of a 15-day pretreatment with cocaine 5 and 10 mg/kg s.c. but not with 20 mg/kg (Fig. 3A). Conversely, pretreatment with cocaine at 10 and 20 mg/kg but not with 5 mg/kg, increased SCH23390 catalepsy 14 days after cocaine with all challenge doses of SCH23390 except 1.0 mg/kg s.c. The cocaine potentiation of SCH23390 cataleptic effects was dose-dependent (Fig. 3B).

The cataleptic effects of haloperidol (0.1–0.5 i.p.) were significantly increased when it was given 1 day after the last dose of a 15-day pretreatment with co-

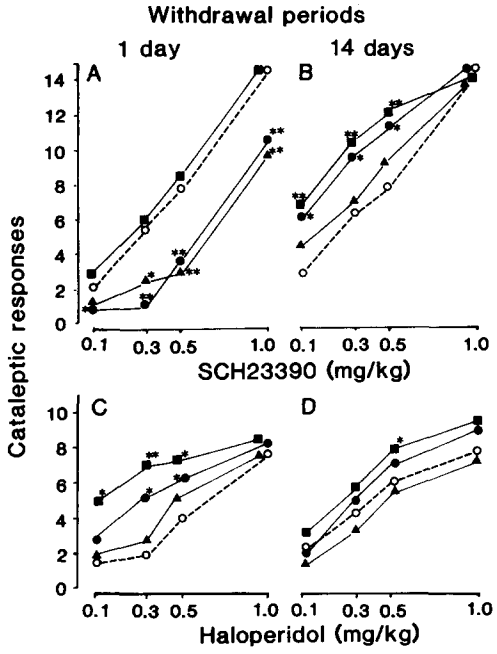

Fig. 3. Dose-related effects of catalepsy in response to SCH23390 and haloperidol in cocaine-pretreated mice. Mice received cocaine (5–20 mg/kg s.c.) once every other day for 15 days (8 injections). SCH23390 (0.1–1.0 mg/kg i.p.) and haloperidol (0.1–1.0 mg/kg i.p.) were administered 1 day and 14 days after the cocaine or saline pretreatments. We observed the cataleptic responses 15 min after challenge dose of SCH23390, and 30 min after that of haloperidol, for 15 min. Saline (open circles), cocaine 5 mg/kg (closed triangles), cocaine 10 mg/kg (closed circles), cocaine 20 mg/kg (closed squares). ** $P < 0.002$, * $P < 0.05$ as compared to saline-injected group

caine at 10 and 20 mg/kg s.c., except for the 1.0 mg/kg i.p. challenge dose of haloperidol. In mice pretreated with 5 mg/kg cocaine, none of the challenge doses of haloperidol produced significant potentiation of the cataleptic response. As with SCH23390, the potentiation of haloperidol catalepsy was greater in animals pretreated with the higher doses of cocaine (Fig. 3C). On the other hand, after 14-day pretreatment with cocaine (5–20 mg/kg s.c.), haloperidol catalepsy was no longer potentiated except for the haloperidol (0.5 mg/kg) response in the 20 mg/kg cocaine-pretreated mice (Fig. 3D).

4. Discussion

Chronic exposure (15-day treatment) to cocaine (5, 10 and 20 mg/kg) produced a shift to the right and left of the dose-response curve of catalepsy to SCH23390 and haloperidol, respectively, during the early withdrawal period. These results demonstrate that the 15-day treatment of mice with cocaine resulted in a decreased and increased sensitivity to the cataleptic actions of SCH23390 and haloperidol, respectively, during the early withdrawal period. This decrease in cataleptic response to SCH23390 after exposure to cocaine (5 and 10 mg/kg) for 15 days could be interpreted as development of supersensitivity of dopamine D_1 receptors, which corresponds to the development of sensitization to cocaine. The increase in haloperidol catalepsy after exposure to cocaine (10 and 20 mg/kg) may represent a state of subsensitivity of dopamine D_2 receptors, which corresponds with the development of tolerance to cocaine. This would indicate that the dopamine D_1 receptor may be the receptor involved in psychostimulant-induced sensitization. However, in the 7-day pretreatment course, the cataleptic effects of both SCH23390 and haloperidol were significantly decreased at the early withdrawal periods (1- and 7-day intervals). These results are consistent with those of a previous study in mice (Hirabayashi et al., 1992) that demonstrated maximum sensitization to ambulation-increasing effects of cocaine following 3–4 injections of cocaine (10 mg/kg) at intervals of 3–7 days. That is, dopamine D_1 and D_2 receptor activities interact synergistically to stimulate locomotor activity (Arnt et al., 1987); locomotor activity mainly depends on the activation of the dopamine D_1 receptor (Starr and Starr, 1988). It has been reported that chronic dopamine D_2 receptor stimulation by dopamine D_2 receptor agonists such as quinpirole (Braun and Chase, 1988) and bromocriptine (Globus et al., 1982) produces subsensitization, whereas chronic dopamine D_1 receptor agonist, SK&F38393, administration produces supersensitivity (Braun and Chase, 1988). The behavioral sensitization induced by chronic exposure to an indirect dopamine receptor agonist such as cocaine may involve mainly dopamine D_1 receptor supersensitivity. Furthermore, chronic administration of dopamine precursors, such as L-dopa, enhances dopamine-sensitive adenyl cyclase activity (Parenti et al., 1986), suggesting that the sensitivity of the dopamine D_1 receptor-coupled cyclase might be increased.

Chronic cocaine (10 mg/kg, twice daily) altered dopamine output compared to that in vehicle-injected rats, inducing a pronounced increase in the first 3 days followed by a clear-cut decrease. This reduction in the output of dopamine during chronic cocaine as well as during withdrawal may be the neurochemical substrate for the addictive properties of cocaine (Imperato et al., 1992). Furthermore, it has been reported that repeated cocaine administration to rats depletes striatal and mesolimbic tyrosine hydroxylase activity 60 days after the last injection (Trulson et al., 1987), without exerting amphetamine-like neurotoxicity (Kleven et al., 1988). This implies that the decreased SCH23390 catalepsy (4 injections) correlates with the increased dopamine, and the increased cataleptic effects (especially SCH23390 catalepsy) correlate with the reduction of dopamine output, based on tyrosine hydroxylase depletion during long-term cocaine treatment as well

as during long-term withdrawal. It suggests that the behavioral actions of chronic cocaine may be dependent on the role of dopamine D_1 receptors more than on that of dopamine D_2 receptors.

In this study, a shift to the left of the dose-response curve of the cataleptic effects to SCH23390 was produced during the longer withdrawal period (14 days) after the higher dose of pretreatment with cocaine. A prolonged withdrawal period after chronic cocaine treatment may be necessary for development of a long-lasting subsensitivity of dopamine D_1 receptors. Kleven et al. (1990) reported that decreases in dopamine D_1 receptor binding (labeled with [^{125}I]-SCH23982) in cortex and striatum were obtained at 2 weeks, but not 20 min, after the last dose of cocaine given for 15 days, whereas changes in dopamine D_2 receptor binding were not observed at 2 weeks after treatment. In addition to the subsensitivity of dopamine D_1 receptors, dopamine D_2 receptors were also rendered subsensitive by chronic cocaine plus a prolonged withdrawal period (for 3 weeks). Furthermore, because of the evidence that the inhibitory effects (cataleptic effects) of SCH23390 on dopamine D_1 receptors may involve a dopamine D_1 receptor-mediated indirect inhibition of dopamine D_2 receptor function (Ushijima et al., 1995; unpublished observation), this implies that during this withdrawal period (for 3 weeks), a dopamine D_1 or D_2 receptor antagonist would not be effective as an antipsychotic drug, and may instead aggravate the subsensitive state.

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