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Development of Tolerance and Reverse Tolerance to Haloperidol- and SCH23390-Induced Cataleptic Effects During Withdrawal Periods After Long-Term Treatment

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USHIJIMA, I., Y. MIZUKI AND M. YAMADA. *Development of tolerance and reverse tolerance to haloperidol- and SCH23390-induced cataleptic effects during withdrawal periods after long-term treatment.* PHARMACOL BIOCHEM BEHAV **50**(2) 259-264, 1995. – The development of tolerance and reverse tolerance and reverse tolerance to the cataleptic effects of selective D_1 antagonist, SCH23390, and the mainly D_2 antagonist, haloperidol, was investigated in mice that had been chronically treated (7 or 30 days) with haloperidol (1 mg/kg SC), SCH23390 (0.5 mg/kg SC), or saline (5 ml/kg SC). In control animals, SCH23390 (0.1–1.0 mg/kg IP) and haloperidol (0.1–1.0 mg/kg IP) produced cataleptic responses in a dose-dependent manner, although the responses had different time course profiles. SCH23390 catalepsy had a rapid onset but a short duration, whereas haloperidol catalepsy had a slower onset and longer duration. This could be due to differences in lipid solubility of the drugs, or at least pertly to an action of the drugs on different neuronal pathways. The cataleptic effects of SCH23390 (0.3 mg/kg IP) and haloperidol (0.3 mg/kg IP) were significantly reduced in mice when given 24 h, but not 72 h, after the last dose of a 7 day-pretreatment course (short-term treatment) of SCH23390. However, after long-term treatment (30 days) with SCH23390, a challenge dose of SCH23390 exhibited reverse tolerance (i.e., increased catalepsy) when given 7–21 days, but not 1–3 days, after the last injection of the SCH23390 pretreatment course. In contrast, haloperidol catalepsy was not affected by long-term SCH23390 treatment. However, after the last dose of long-term haloperidol treatment both SCH23390 and haloperidol exhibited tolerance to their cataleptic effects at 1–3 days, a normal response at 7 days, and an exaggerated response (reverse tolerance) at 15–21 days. These results suggest that a prolonged withdrawal period after chronic D_1 antagonist treatment is necessary for the development of reverse tolerance to a D_1 antagonist (an increase in catalepsy), which may be a reflection of a long-lasting subsensitivity of D_1 receptors. Long-term treatment with a D_2 receptor antagonist caused supersensitivity of D_1 and D_2 receptors during the early withdrawal period and subsensitivity after a longer period of withdrawal. These results also provide evidence that the cataleptic effects of SCH23390 may be mediated by indirect blockade of D_2 receptor function through its D_1 blocking action, whereas the cataleptic effects of haloperidol may be affected by supersensitivity of D_1 receptors, but not by their subsensitivity.

Haloperidol, SCH23390 Catalepsy Chronic treatment Tolerance Reverse tolerance Mice

CHRONIC treatment with neuroleptic drugs has been shown to reduce the frequency of psychotic episodes in schizophrenic patients (9). The use of these drugs, however, is limited because of the frequent development of tardive dyskinesia (1). The clinical efficacy of the neuroleptics is based in their ability to block dopamine receptors. Chronic blockade of dopamine receptors results in an increase in receptor number, which restores dopaminergic neurotransmission (19). It would thus

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be of great clinical benefit to develop antipsychotic agents that did not also promote such changes in receptor sensitivity.

One of the behavioral tests for neuroleptic activity is to measure the ability of a drug to induce a cataleptic state in rodents (6,18). It has been postulated that neuroleptic catalepsy results from the blockade of dopamine receptors in the neostriatum (10,11,13,16,29) and nucleus accumbens (13). The cataleptic effects induced by SCH23390 and haloperidol share common features—that is, both can be suppressed by muscarinic antagonists and by D_2 receptor agonists (25, 27,28,35). Furthermore, D_1 and D_2 receptor antagonists potentiate each other's effect in producing catalepsy, or the presence of synergistic effects between D_1 and D_2 receptor blockade (36).

However, after chronic treatment, tolerance develops to the cataleptic effects of haloperidol (3,12), whereas no tolerance has been observed with chronic SCH23390 administration in rats even after 3 weeks of treatment (14,15). Lappalainen et al. (24) reported that repeated treatment with SCH23390 and haloperidol induced differential tolerance to the cataleptic effects of these antagonists. Initial tolerance to the higher SCH23390 dose regimen occurred after 6 days and disappeared afterward. This reversal of tolerance was not seen in the haloperidol-treated group. The purpose of the present study was to investigate how withdrawal conditions after the chronic administration of D_1 and D_2 receptor antagonists differentially influence the cataleptic effects of SCH23390 and haloperidol.

METHOD

Animals

Healthy male Deutschland Densenbyo Yoken (ddY) albino mice (4–7 weeks, 20–35 g), purchased from Kyudo Animal Laboratory (Kumamoto, 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 (lights on at 0700 h; lights off at 1900 h). We used 7-week-old mice for a 7-day pretreatment and 4-week-old mice for a 30-day pretreatment at the start of the study. All experiments were performed by using 8- or 9-week-old mice weighing 35–40 g.

Measurement of Catalepsy

Catalepsy was measured by means of the bar method, by placing mice individually on a plastic board (25–35 cm) with a horizontal wire bar (3 mm in diam., sealed with vinyl) suspended 5 cm above the floor. We used 10 devices with 10 stopwatchs to ensure methodic observation. The observers were blinded with respect to treatment. 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. 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

To observe the dose and temporal properties of the cataleptic responses to SCH23390 and haloperidol, we administered SCH23390 (0.1–1.0 mg/kg IP) or haloperidol (0.1–1.0 mg/kg IP) to naive mice (10 mice per group) (Fig. 1).

Table 1 shows the schedule of chronic drug treatment. Mice used in the drug interaction studies received haloperidol (1.0 mg/kg SC), SCH23390 (0.5 mg/kg SC), or saline (5 ml/kg SC) once a day for 7 (Experiments I and II) or 30 (Experiments III and IV) days. The injection followed by behavioral observation were carried out every day at 1000 h for haloperidol, at 1100 h for saline, and at 1300 h for SCH23390. To observe the cataleptic effects, we administered haloperidol (0.3 mg/kg IP) or SCH23390 (0.3 mg/kg IP) at 1.5-min intervals 1, 3, 7, 15, or 21 days after the last injection of the pretreatment regimen. We used the same mice on days 1 and 15, and on days 3 and 21. The experiments in Figs. 2A and 3A (n = 99), in Figs. 2B and 3B (n = 99), in Figs. 4A and 5A (n = 99), and in Figs. 4B and 5B (n = 99) were carried out on same days. The chronic saline data in Figs. 2 and 3 and in Figs. 4 and 5 were same.

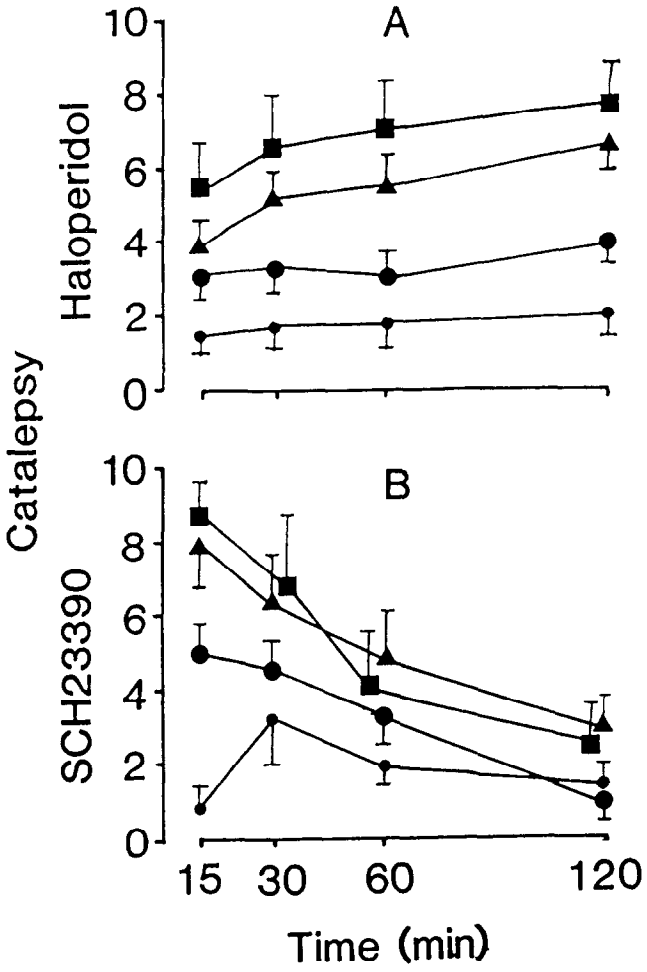

FIG. 1. Dose responses of catalepsy to haloperidol (A) and SCH23390 (B), 0.1 mg/kg IP; ●, 0.3 mg/kg IP; ▲, 0.5 mg/kg IP; ■, 1.0 mg/kg.

Drugs

The drugs used were (R)-(+)-SCH23390 (RBI, Natick, MA) and haloperidol (Dainippon, Osaka, Japan).

Statistics

The data are expressed as mean ± SE. Each group consisted of a minimum of 10 animals. The significance of differences of between-group data were analyzed using Mann-Whit-

TABLE 1

EXPERIMENTAL SCHEDULES

Exp.	Doses of Drugs (mg/kg SC)	Withdrawal Period (days)	Challenge Dose of Drug (mg/kg IP)	No.	Fig.
I	a. Haloperidol (1) × 7	1, 15	Haloperidol (0.3)	11	2A
	SCH23390 (0.5) × 7	1, 15	Haloperidol (0.3)	11	3A
	Saline (5 ml/kg) × 7	1, 15	Haloperidol (0.3)	11	2A, 3A
	b. Haloperidol (1) × 7	3, 21	Haloperidol (0.3)	11	2A
	SCH23390 (0.5) × 7	3, 21	Haloperidol (0.3)	11	3A
	Saline (5 ml/kg) × 7	3, 21	Haloperidol (0.3)	11	2A, 3A
	c. Haloperidol (1) × 7	7	Haloperidol (0.3)	11	2A
	SCH23390 (0.5) × 7	7	Haloperidol (0.3)	11	3A
	Saline (5 ml/kg) × 7	7	Haloperidol (0.3)	11	2A, 3A
II	a. Haloperidol (1) × 7	1, 15	SCH23390 (0.3)	11	2B
	SCH23390 (0.5) × 7	1, 15	SCH23390 (0.3)	11	3B
	Saline (5 ml/kg) × 7	1, 15	SCH23390 (0.3)	11	2B, 3B
	b. Haloperidol (1) × 7	3, 21	SCH23390 (0.3)	11	2B
	SCH23390 (0.5) × 7	3, 21	SCH23390 (0.3)	11	3B
	Saline (5 ml/kg) × 7	3, 21	SCH23390 (0.3)	11	2B, 3B
	c. Haloperidol (1) × 7	7	SCH23390 (0.3)	11	3B
	SCH23390 (0.5) × 7	7	SCH23390 (0.3)	11	2B
	Saline (5 ml/kg) × 7	7	SCH23390 (0.3)	11	2B, 3B
III	a. Haloperidol (1) × 30	1, 15	Haloperidol (0.3)	11	4A
	SCH23390 (0.5) × 30	1, 15	Haloperidol (0.3)	11	5A
	Saline (5 ml/kg) × 30	1, 15	Haloperidol (0.3)	11	4A, 5A
	b. Haloperidol (1) × 30	3, 21	Haloperidol (0.3)	11	4A
	SCH23390 (0.5) × 30	3, 21	Haloperidol (0.3)	11	5A
	Saline (5 ml/kg) × 30	3, 21	Haloperidol (0.3)	11	4A, 5A
	c. Haloperidol (1) × 30	7	Haloperidol (0.3)	11	4A
	SCH23390 (0.5) × 30	7	Haloperidol (0.3)	11	5A
	Saline (5 ml/kg) × 30	7	Haloperidol (0.3)	11	4A, 5A
IV	a. Haloperidol (1) × 30	1, 15	SCH23390 (0.3)	11	4B
	SCH23390 (0.5) × 30	1, 15	SCH23390 (0.3)	11	5B
	Saline (5 ml/kg) × 30	1, 15	SCH23390 (0.3)	11	4B, 5B
	b. Haloperidol (1) × 30	3, 21	SCH23390 (0.3)	11	4B
	SCH23390 (0.5) × 30	3, 21	SCH23390 (0.3)	11	5B
	Saline (5 ml/kg) × 30	7	SCH23390 (0.3)	11	4B, 5B
	c. Haloperidol (1) × 30	7	SCH23390 (0.3)	11	4B
	SCH23390 (0.5) × 30	7	SCH23390 (0.3)	11	5B
	Saline (5 ml/kg) × 30	7	SCH23390 (0.3)	11	4B, 5B

The experiment (Exp.) was divided into four sections (I-IV). After the final treatment, the balanced mice (35–40 g) received a challenge dose of haloperidol (0.3 mg/kg IP) or SCH23390 (0.3 mg/kg IP). We observed cataleptic responses 15, 30, 60, and 120 min after haloperidol or SCH23390.

ney *U*-tests. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Dose-Related Effects of Catalepsy to SCH23390 and Haloperidol

The cataleptic response to an acute dose of haloperidol (0.1–1.0 mg/kg IP) appeared slowly and was more prolonged compared with SCH23390. The cataleptic effect of haloperidol exhibited dose dependency, was most prominent at 30 min to 2 h, and persisted for more than 3 h (Fig. 1A). SCH23390 (0.1–1.0 mg/kg IP) produced a dose-related cataleptic effect of rapid onset and short duration with maximal effects peaking within 15–30 min of the injection (Fig. 1B).

Effects of Duration of Antagonist Exposure and Period of Withdrawal on the Cataleptic Responses to Challenge Doses of SCH23390 and Haloperidol

In mice pretreated with haloperidol for 7 days, an attenuated cataleptic response at 24 h of withdrawal was produced by a challenge dose of haloperidol or SCH23390, which was restored to normal by days 3 and 7, respectively (Fig. 2). Twenty-four, but not 72, h after a 7-day treatment regimen with SCH23390, a challenge dose of haloperidol produced an attenuated cataleptic response. However, the cataleptic response to a challenge dose of SCH23390 remained attenuated for 24 and 72 h, but had returned to normal levels by day 7 after the last pretreatment dose of SCH23390 (Fig. 3).

In mice given long-term (30 days) treatment with haloperi-

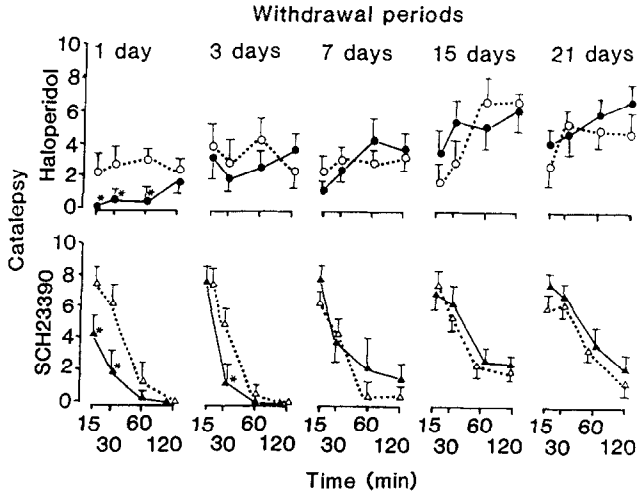

FIG. 2. Effects of withdrawal periods after 7 days of treatment with haloperidol or saline on cataleptic responses induced by haloperidol (0.3 mg/kg IP) or SCH23390 (0.3 mg/kg IP). Mice received haloperidol (1.0 mg/kg SC) or saline (5 ml/kg SC) once a day for 7 days, and then received haloperidol (0.3 mg/kg IP) and SCH23390 (0.3 mg/kg IP) 1, 3, 7, 15, or 21 days later. Haloperidol catalepsy: ○, chronic saline; ●, chronic haloperidol. SCH23390 catalepsy: △, chronic saline; ▲, chronic haloperidol. *$p < 0.05$ compared with the saline-injected group.

dol (1 mg/kg SC daily), a challenge dose of either haloperidol or SCH23390 produced an attenuated cataleptic response during days 1-3, a normal response on day 7, and a potentiated response on days 14-21 of withdrawal (Fig. 4). In contrast, after 30 days of pretreatment with SCH23390, mice responded with a potentiated cataleptic response during days 7-21, but not days 1-3, to a challenge dose of SCH23390, whereas the

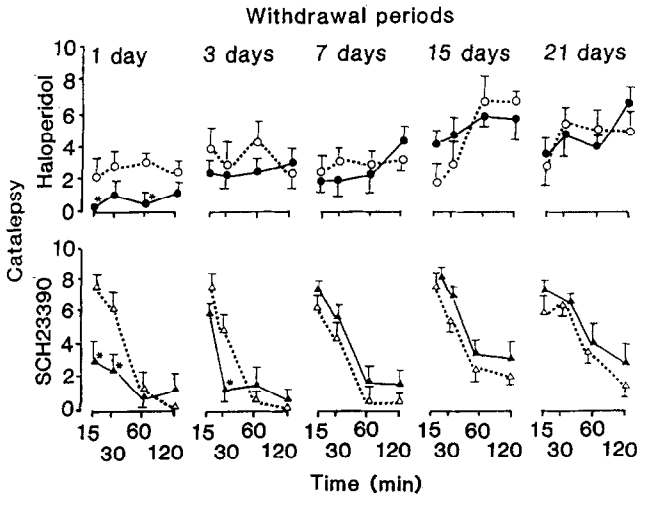

FIG. 3. Effects of withdrawal periods after 7 days of treatment with SCH23390 or saline on cataleptic responses induced by haloperidol and SCH23390. Mice received SCH23390 (0.5 mg/kg SC) or saline (5 ml/kg) once a day for 7 days. Haloperidol catalepsy: ○, chronic saline; ●, chronic SCH23390. SCH23390 catalepsy: △, chronic saline; ▲, chronic SCH23390. Other details as in Fig. 2.

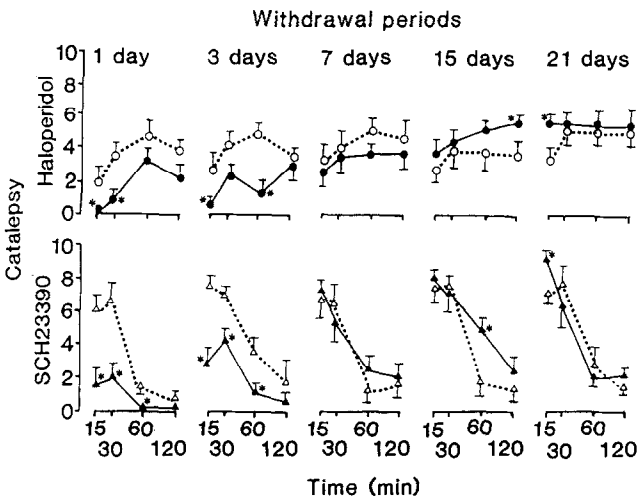

FIG. 4. Effects of withdrawal periods after 30 days of treatment with haloperidol or saline on cataleptic responses induced by haloperidol and SCH23390. Mice received haloperidol (1.0 mg/kg SC) or saline once a day for 30 days. Other details as in Fig. 2.

cataleptic effects of a challenge dose of haloperidol were unaltered at any time after the long-term pretreatment with SCH23390 (Fig. 5).

DISCUSSION

We demonstrated in this study that the acute treatment of mice with haloperidol and SCH23390 produced dose-dependent cataleptic responses that differed in their temporal properties. The haloperidol catalepsy had a slower onset and longer duration, and the SCH23390 catalepsy had a rapid onset but a short duration. These results are compatible with those of a previous report (24). The temporal pattern of cata-

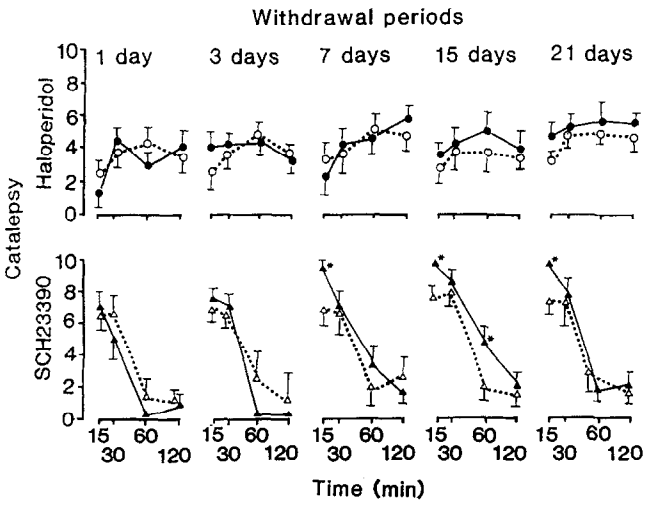

FIG. 5. Effects of withdrawal periods after 30 days of treatment with SCH23390 or saline on cataleptic responses induced by haloperidol and SCH23390. Mice received SCH23390 (0.5 mg/kg SC) or saline once a day for 30 days. Other details as in Fig. 3.

lepsy did not change after chronic treatment with either SCH23390 or haloperidol. We suggest that different neuronal pathways are responsible for the cataleptic responses evoked by blockade of D_1 and D_2 receptors.

During the first 3 days after discontinuation of short-term (7 days) treatment with SCH23390 or haloperidol, challenge doses of either drug exhibited attenuated cataleptic responses, indicating that tolerance had developed (Figs. 2 and 3). However, in animals given long-term (30 days) pretreatment of SCH23390 or haloperidol, we observed drug-dependent and time-dependent changes in the responses to subsequent doses of SCH23390 or haloperidol. Long-term haloperidol pretreatment induced tolerance to the cataleptic effects of subsequent SCH23390 or haloperidol challenge during days 1-3 of withdrawal. This tolerance effect disappeared by day 7 and converted to a reverse tolerance response (increased catalepsy) during days 14-21 of withdrawal. In sharp contrast, after long-term SCH23390 pretreatment, only reverse tolerance of the cataleptic response to SCH23390 challenge was seen during days 7-21 after the last dose of SCH23390 pretreatment. Neither tolerance nor reverse tolerance effects were seen with a challenge dose of haloperidol at any time point investigated. These results indicate that the catalepsy mediated by D_1 inhibition may be affected by altering D_2 receptor sensitivity (either super- or subsensitivity), whereas that mediated by D_2 receptor inhibition may be modified by supersensitive, but not subsensitive, D_1 receptor changes. Accordingly, SCH23390 catalepsy may be mediated by indirect blockade of D_2 receptor function through its D_1 blocking action, whereas haloperidol catalepsy is mediated by direct blockade of D_2 receptors. A chronic (long-term) inhibition of D_1 receptors followed by a prolonged withdrawal period appears to be necessary for the development of reverse tolerance effects (increase in catalepsy) to a subsequent administration of a D_1 receptor antagonist. This increased (potentiated) cataleptic response may be a reflection of the D_1 antagonist acting on a D_1 receptor system rendered subsensitive by the chronic SCH23390 along with the prolonged withdrawal period. In contrast, shortly after chronic inhibition of D_2 receptors, supersensitivity of these receptors could be produced, which might contribute to the tolerance response (decreased catalepsy) produced by a challenge dose of either SCH23390 or haloperidol—that is, the supersensitive D_2 system opposes the normal effect of the challenge antagonist. The reverse tolerance seen at the later times (15-21 days) after long-term haloperidol pretreatment may be explained on the basis of the challenge D_1 or D_2 antagonist acting on a subsensitive D_2 system.

Classical neuroleptics such as haloperidol induce the upregulation of striatal D_2 receptors (15). However, several authors have reported selective upregulation of D_1 receptors after chronic (12-21 days) SCH23390 treatment followed by a 2-8-day withdrawal period (8,14,15,26), although this was not confirmed by Hyttel (17). Lappalainen et al. (23) also observed no changes in the density of D_1 receptors 16 h after 18 days of SCH23390 treatment. Perhaps this finding is due to the short time interval (16 h) between decapitation and the final injection of SCH23390. There may be differences among the antipsychotic drugs as to how long the administration and withdrawal periods must be for full expression of the up- and down-regulated dopamine receptors to occur. Although SCH23390 (0.1 mg/kg IP) is cleared rapidly from the plasma, high levels are maintained in the CNS for comparatively long periods of time (30). The stimulation of adenylyl cyclase by dopamine was attenuated in rat striatal homogenates treated with SCH23390 as much as 12 h before sacrifice. On the other hand, the plasma half-life of haloperidol is rather long (7). It has been reported for haloperidol that blood and brain levels peak and decline over very similar time courses (7). Accordingly, it is likely that the dopamine receptors in the brains of mice receiving either chronic SCH23390 or haloperidol are continuously exposed to the drugs during the 24-h period before the next injection of the drugs. However, in the chronic studies (Figs. 2-5), 24 h after the last injection, the cataleptic actions of haloperidol and SCH23390 were unchanged from those of the drug näive mice (Fig. 1). Thus, the differential changes of haloperidol and SCH23390 during withdrawal could result from either differences in their half-lives or differences in receptor sensitivities.

On the other hand, it has been suggested that depolarization inactivation of the A10 dopamine neurons is related to the antipsychotic effect of neuroleptics, whereas depolarization inactivation of the A9 dopamine neurons is causally related to the development of the extrapyramidal symptoms (4,5). The concept of depolarization inactivation provides a good model for the further understanding of therapeutic efficacy and extrapyramidal symptoms in the treatment of schizophrenia. Depolarization inactivation of the A9 and A10 dopamine cells would alter dopamine release from their nerve terminals in striatum and accumbens, respectively. Chronic haloperidol appears to decrease dopamine release in nigrostriatal and mesolimbic dopaminergic systems, whereas SCH23390 decreases dopamine metabolism (homovanillic acid concentrations) in nucleus caudatus, but not in nucleus accumbens (21,22). The decrease in dopamine release may be due to the development of depolarization inactivation of dopamine cells (2,21,22). If the development of supersensitivity of dopamine receptors to the neuroleptics plays a role in extrapyramidal side effects, the effect is most likely to occur at D_2 receptors in striatum. Although the clinical potency of neuroleptics correlates with their affinity for D_2 receptors (31,32), the therapeutic efficacy of neuroleptics in the treatment of schizophrenia may be caused by subsensitivity of D_1 receptors, which are rich in nucleus accumbens (33).

It has been shown that methamphetamine-induced sensitization can be blocked by the coadministration of haloperidol or SCH23390 (20,34). We also found that animals treated chronically with methamphetamine responded with a decreased SCH23390 catalepsy (supersensitivity of D_1 receptors) and with an increased haloperidol catalepsy (subsensitivity of D_2 receptors). The decreasing and increasing cataleptic effects of SCH23390 and haloperidol, respectively, after chronic methamphetamine were prevented by the coadministration of either SCH23390 or haloperidol (unpublished observation). Based on its ability to suppress the development of behavioral sensitization to chronic methamphetamine, which has been considered to be a model of schizophrenia, a D_1 receptor antagonist may represent a potentially new antipsychotic drug devoid of extrapyramidal symptoms.

Long-term treatment with SCH23390 or haloperidol causes numerous neurochemical changes (e.g., GABA, glutamate, serotonin, noradrenaline, acetylcholine). Further studies are required to define whether the changes of other neurotransmitter systems are associated with the effects of chronic SCH23390 and haloperidol on the dopaminergic D_1 and D_2 receptors.

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