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D_1 and D_2 Dopamine Receptor-Mediated Mechanisms and Behavioral Supersensitivity

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MARIN, C., S. A. PARASHOS, V. KAPITZOGLOU-LOGOTHETIS, A. PEPPE AND T. N. CHASE. *D_1 and D_2 dopamine receptor-mediated mechanisms and behavioral supersensitivity.* PHARMACOL BIOCHEM BEHAV **45**(1) 195–200, 1993.—The contribution of D_1 and D_2 dopamine (DA) receptor mechanisms to the behavioral supersensitivity and receptor upregulation induced by chronic DA antagonist administration were compared. Rats received either the selective D_1 DA receptor antagonist SCH23390, the selective D_2 DA receptor antagonist raclopride, their combination, or haloperidol, a predominantly D_2 antagonist, for 21 days. Equivalent cataleptogenic doses of all drugs and drug combinations were employed. Tolerance to the cataleptic response was observed only in the haloperidol-treated group. Apomorphine-induced stereotypies were significantly enhanced in SCH23390-, raclopride-, and haloperidol-treated rats. In contrast, coadministration of both SCH23390 and raclopride had no effect on apomorphine-induced stereotypy. These findings suggest that neuroleptics blocking in equal proportion D_1 and D_2 receptor sites might be less likely to induce tardive dyskinesia and drug tolerance than those acting selectively on one or the other of these receptor subtypes.

Dopamine receptor interactions Neuroleptics Tardive dyskinesia Catalepsy Behavioral supersensitivity

TARDIVE dyskinesia is a syndrome characterized by abnormal involuntary movements, usually involving the oral and sometimes the limb and truncal musculature, that arises after prolonged use of antipsychotic drugs. Preclinical and clinical evidence suggest that a proliferation of postsynaptic dopamine (DA) receptors in the nigrostriatal pathway contributes to the pathogenesis of this disorder (20,33).

In the experimental animal, repeated administration of neuroleptics for several weeks, followed by drug withdrawal, leads to DA receptor upregulation and behavioral supersensitivity as manifested by an increase in dopamine agonist-induced stereotypies (21). Numerous studies suggest that these neuroleptic effects, proposed as an animal model of tardive dyskinesia (1), are mediated by their blocking action at D_2 DA receptors (7). Although long-term administration of the D_1-selective antagonist SCH23390 produces D_1 receptor upregulation (8,32), the contribution of D_1 receptor-mediated mechanisms to the pathogenesis of tardive dyskinesia has yet to be established. Behavioral studies support the hypothesis that a close functional interaction exists between D_1 and D_2 receptor-mediated mechanisms. In rats with a unilateral quinolinic acid lesion of the striatum, the selective D_1 agonist SK&F38393 does not induce rotation when administered alone but does increase turning elicited by the D_2 agonist LY 171555 in a dose-dependent manner (2). The hypersensitive stereotyped behavior resulting from chronic neuroleptic treatment does not, however, exhibit D_1/D_2 synergism. Stereotypy induced by chronic treatment with both the D_1-selective antagonist SCH23390 and the predominantly D_2 antagonist haloperidol is no greater than that produced by chronic treatment with either drug alone (29).

Neuroleptics mediate certain behavioral responses that correlate closely with their potency as antidopaminergic and antipsychotic drugs (35). One such behavior is catalepsy or the relative immobility of animals when placed in an abnormal posture (26). Both D_1 and D_2 antagonists can produce catalepsy (6,28) and there is a synergistic effect when D_1 and D_2 antagonists such as SCH23390 and raclopride are coadministered (31).

As an approach toward improving neuroleptic therapy by

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maximizing antipsychotic activity while minimizing extrapyramidal side effects, we compared the effects of chronic treatment with a selective D_1 antagonist, a selective D_2 antagonist, and their combination with those of haloperidol on catalepsy and stereotyped behavior.

METHOD

Animals

Male Sprague-Dawley rats (Taconic Farms) initially weighing between 220–240 g were used in all experiments. They were housed four per cage in a temperature- and humidity-controlled room under a 12 L : 12 D cycle with food and water ad lib.

Drugs

SCH23390 (Schering, Bloomfield, NJ) was dissolved in a minimum volume of 0.5% lactic acid in normal saline; raclopride tartrate (Astra, Sodertälje, Sweden) was diluted in saline; haloperidol (McNeil Pharmaceuticals, Spring House, PA) was diluted in distilled water; apomorphine HCl (Sigma Chemical Co., St Louis, MO) was dissolved in a 0.2% ascorbic acid solution.

Treatment Schedules

Minimal cataleptogenic doses were obtained from dose-response curves after a single dose of neuroleptic administration. Five animals were used for each dose.

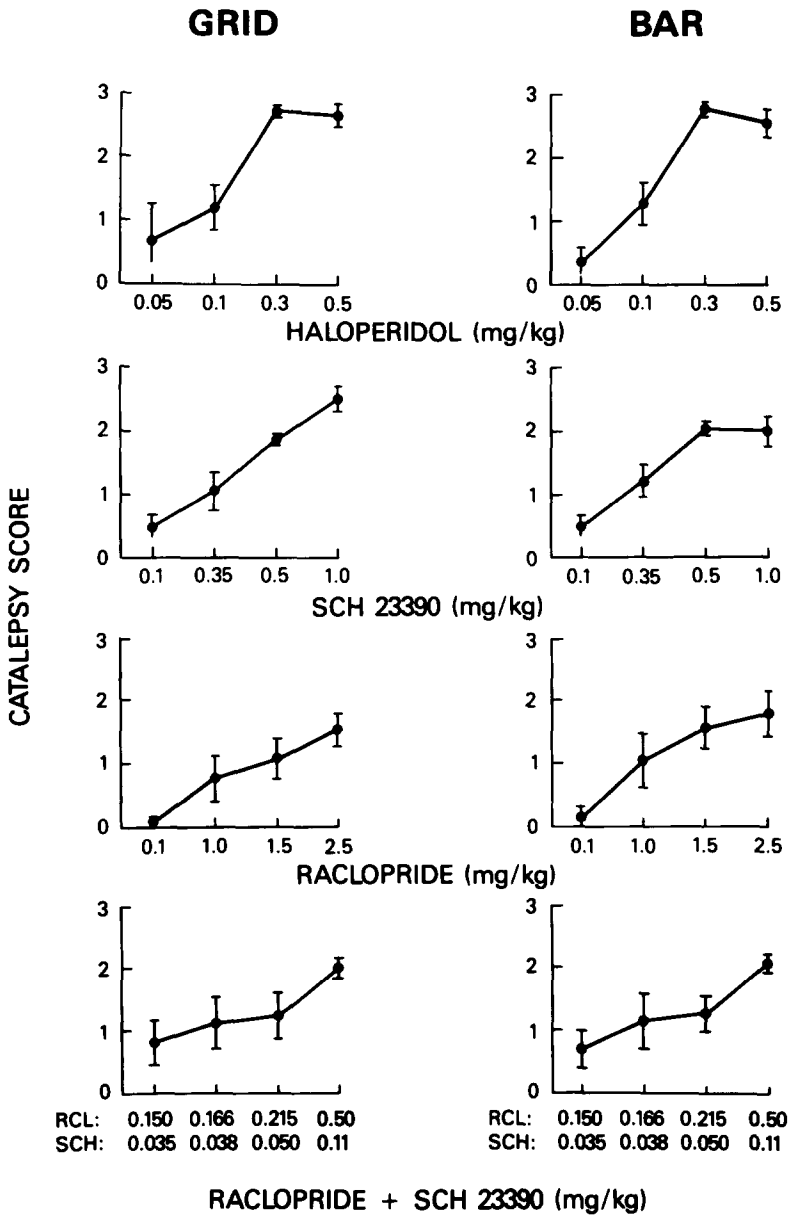

FIG. 1. Dose-response curves for cataleptic effects of haloperidol, SCH23390, raclopride, and the combination of raclopride and SCH23390. Minimal cataleptogenic dose was selected for a score of 1. Each point represents the mean catalepsy score (±SEM) for five animals.

Measurement of catalepsy was done on days 1 and 21 of treatment with the minimal cataleptogenic doses. Five groups of eight animals were injected for 21 days with one of the following drugs: raclopride (1.5 mg/kg, IP), SCH23390 (0.35 mg/kg, SC), raclopride + SCH23390 (0.166 + 0.038 mg/kg, respectively), haloperidol (0.1 mg/kg, SC), or saline (control group). Haloperidol and raclopride were administered once daily at 10:00 a.m. and SCH23390 was given twice daily (half of daily dose in each injection) at 10:30 a.m. and 5:00 p.m. in view of its relatively short plasma half-life (19).

Apomorphine-induced stereotyped activity were evaluated in the same animals after discontinuation of chronic neuroleptic treatment.

Measurement of Catalepsy

Rats were tested for their cataleptic response on days 1 and 21. Two different tests were used: In the vertical grid test, animals were placed on a wire grid inclined 60° to the horizontal plane with all four legs abducted and extended; in the horizontal bar test, the forepaws were placed on a 10-cm high horizontal bar while the hindpaws remained on the floor. The time before a change in position occurred was scored during 2 min every 20 min starting 10 min after drug administration for a total of 150 min on a scale of 0–3: 0 (0–14 s), 1 (15–29 s), 2 (30–59 s), and 3 (60 or more s) (25). At the end of the experiment, mean scores were calculated for each animal. A score of 1 in the grid test was used as the criterion for estimating the minimal cataleptic effective dose (28).

Measurement of Stereotypy

Animals were studied in a quiet room after a 4-day drug washout period. Rats were placed individually in 45 × 24 × 20-cm observation cages with a wire grid on the bottom. After 2 h habituation, animals were injected with apomorphine (29) (0.3 mg/kg, SC), and stereotyped behavior was scored for 10 s every 5 min for 90 min. Motor behavior was evaluated by means of a modified Ernst stereotypy scale (10) scored as follows: 0 = normal behavior seen in animals after saline administration; 1 = continuous locomotor behavior, discontinuous rearing, sniffing, or licking; 2 = moderate locomotor activity, continuous sniffing; 3 = sporadic locomotor activity (restricted to a small area around the animal) with sniffing and licking, occasionally gnawing or chewing (vacuous chewing movements); 4 = continuous licking, gnawing, or biting with occasional locomotor activity.

Statistical Analysis

Statistical differences were evaluated using analysis of variance (ANOVA) followed by two-tailed Dunnett's *t*-test. Paired Student's *t*-test was used for the comparisons between days 1 and 21.

RESULTS

Catalepsy Measurements

Single-dose administration of raclopride or SCH23390 alone or combined, as well as haloperidol, induced a cataleptic response as measured in both the horizontal bar and vertical grid tests (Fig. 1). The minimal cataleptic dose was 0.1 mg/kg for haloperidol, 0.35 mg/kg for SCH23390, and 1.5 mg/kg for raclopride. In animals receiving combined drug treatment, it was necessary to reduce the dose of both SCH23390 and raclopride ninefold to obtain a similar cataleptic response. A positive catalepsy test (score of 1) was never observed in control rats even after repeated testing. Catalepsy produced by SCH23390 had a rapid onset and peaked at 30 min. A similar time course occurred in the combined treatment group. In contrast, haloperidol- or raclopride-induced catalepsy had a slower onset (Fig. 2). Chronic (21 days) treatment produced tolerance in the haloperidol-treated group ($p < 0.05$) but not in the other groups (Fig. 3).

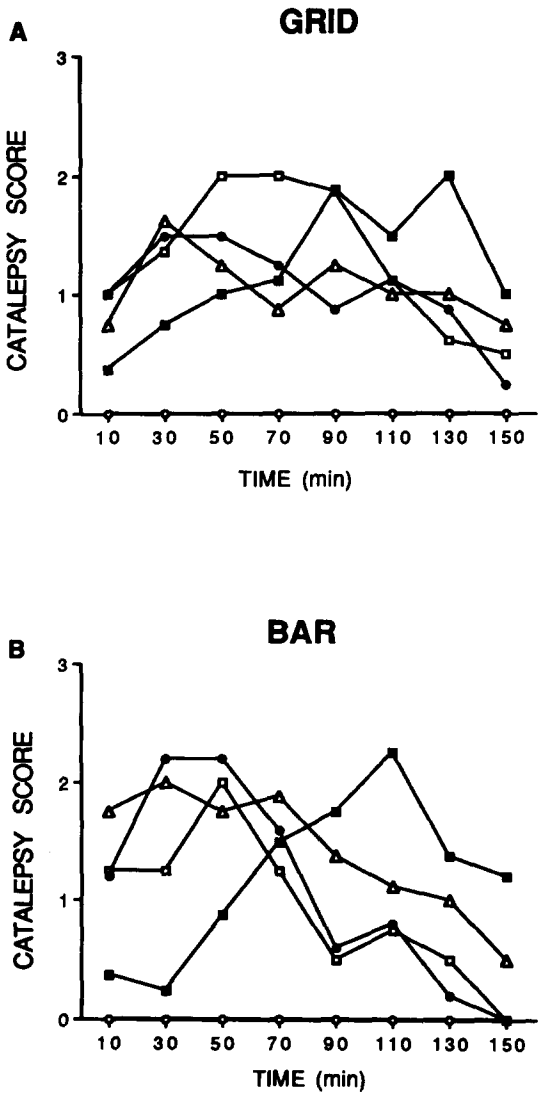

FIG. 2. Time course of the cataleptic response following a single dose of haloperidol (0.1 mg/kg, SC, ■), raclopride (1.5 mg/kg, IP, □), SCH23390 (0.35 mg/kg, SC, ●), raclopride + SCH23390 (0.166 mg/kg, IP, and 0.038 mg/kg, SC, respectively, △), or normal saline (○). Each point represents the mean catalepsy score for five animals. (a) Vertical grid test. (b) Horizontal bar test.

Stereotypy Measurements

Chronic treatment with haloperidol (0.1 mg/kg), SCH23390 (0.35 mg/kg), or raclopride (1.5 mg/kg) enhanced the stereotypy response to apomorphine (Fig. 4). Rats treated with both SCH23390 and raclopride, at doses ninefold lower than used

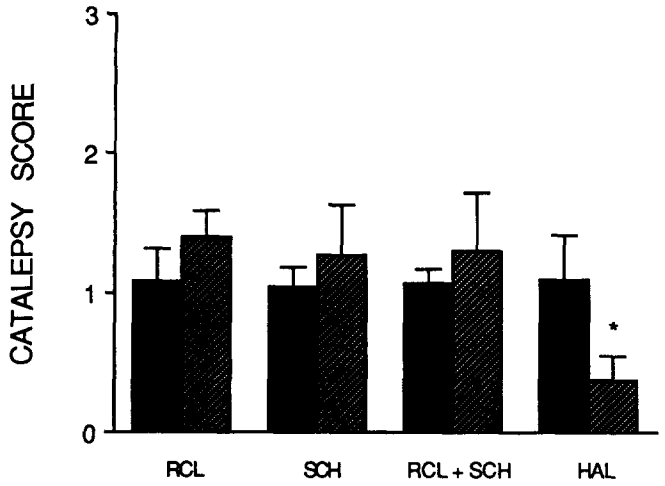

FIG. 3. Cataleptic effects of dopamine antagonists on day 1 (■) and day 21 (□ of treatment: raclopride (1.5 mg/kg), SCH23390 (0.35 mg/kg), raclopride + SCH23390 (0.166 and 0.038 mg/kg, respectively), and haloperidol (0.1 mg/kg). Each point represents the mean catalepsy score (± SEM) for eight animals. *$p < 0.01$ in comparison with day 1.

when these drugs were given alone, showed mean stereotypy scores that were not different from the saline control group.

DISCUSSION

The ability of chronically administered DA receptor antagonists to upregulate DA receptors and increase apomorphine-induced stereotypy is well established (21). These effects are observed with drugs acting nonselectively to block D_1 and D_2 DA receptor subtypes, as well as with drugs acting selectively on either one receptor subtype or the other (7,8). The induction of catalepsy in rodents has long been associated with DA receptor blockade and taken as an index of neuroleptic activity (22). Moreover, brain neuroleptic levels and catalepsy scores correlate closely (5).

The present findings indicate that coadministration of a selective D_1 antagonist, SCH23390, and selective D_2 antagonist, raclopride, leads to a synergistic interaction in their cataleptic effects. This synergism requires a substantial reduction in the doses of both compounds to retain an equivalent cataleptic response to that when the drugs are administered alone. However, although in all treatment groups DA receptors were blocked to a similar degree (in all groups catalepsy score was 1), chronic treatment with the combination of SCH23390 and raclopride did not lead to an increase in apomorphine-induced stereotypy. These results are in agreement with recent findings that chronic treatment with sulpiride and SCH23390, at doses having no effect by themselves, antagonized apomorphine-elicited stereotypy without inducing supersensitivity (9). Haloperidol, after 21 days of treatment, produced a significant decrease in catalepsy, suggesting the development of tolerance in association with the D_2 DA receptor upregulation induced by classic neuroleptics during long-term administration (11,24). Chronic treatment with SCH23390 produced no tolerance to its cataleptogenic effects despite the presence of D_1 DA receptor upregulation, as reported previously (16,17). It is not yet known why rats become tolerant to the cataleptogenic effects of D_2 antagonists but not to those of D_1 antagonists.

Raclopride, differing from haloperidol, did not induce tolerance to catalepsy during chronic treatment. It has previously been observed that raclopride has a low affinity for binding sites labeled by the D_1 antagonist [^{3}H]flupenthixol and does not block DA-stimulated adenylate cyclase (28), suggesting a selective D_2 antagonism in vitro. However, it is possible to speculate that this compound might not maintain its D_2 DA receptor specificity in vivo. Supporting this possibility, it has been observed (18) that D_1 receptor function is altered after chronic administration of the D_2-selective antagonist sulpir-

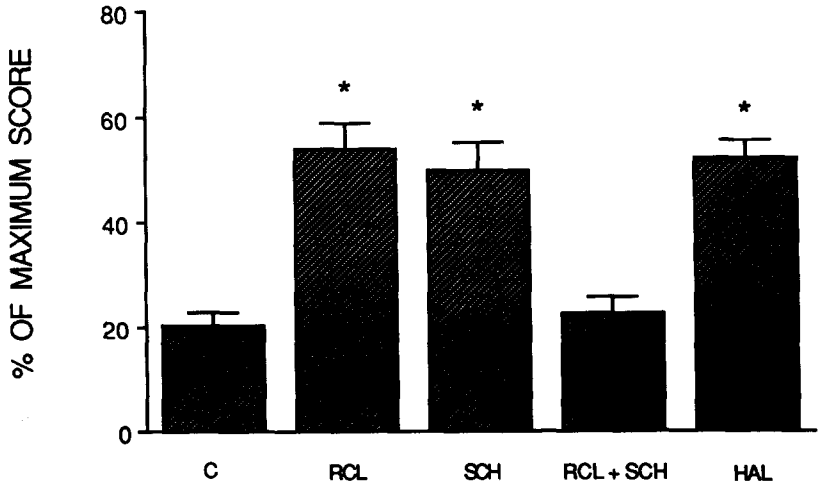

FIG. 4. Comparative effects of chronically administered raclopride (RCL, 1.5 mg/kg), SCH23390 (SCH, 0.35 mg/kg), raclopride + SCH23390 (RCL + SCH, 0.166 and 0.038 mg/kg, respectively), and haloperidol (HAL, 0.1 mg/kg) on apomorphine-induced stereotypy (0.3 mg/kg). Each point represents the mean percentage of maximum score (± SEM) for eight animals. *$p < 0.01$ in comparison with control group.

ide, perhaps indicating that some D_2 antagonists exert an inhibitory effect on D_1 receptors (36). However, sulpiride is a closely related benzamide compound and that loss of selectivity may be a property of benzamides.

Concomitant administration of raclopride and SCH23390 produced a synergism in their cataleptic effects in agreement with earlier observations (23,31); doses of both compounds have to be markedly reduced to obtain a cataleptic effect equivalent to that obtained when either drug is given alone. Tolerance was not observed with the combination of SCH23390 plus raclopride.

Chronic treatment of rats with classic neuroleptics enhances sensitivity to the motor effects of DA agonists (37) and concomitantly increases D_2 DA receptor number (4). These findings have led to the assumption that the increase in D_2 receptors is both necessary and sufficient for the production of behavioral supersensitivity to DA agonists (13). However, in agreement with previous reports, withdrawal from the repeated administration of SCH23390 was followed by an enhanced stereotyped response to apomorphine (14,38). Chronic treatment with the predominantly D_2 receptor antagonist, haloperidol, significantly increased DA agonist-induced stereotypy (15,34). In the present study, a similar increase was observed in raclopride-treated animals. When D_1- and D_2-selective antagonists were coadministered, apomorphine-induced stereotypies remained unaffected.

The present results may merely reflect the ninefold reduction in the doses of coadministered raclopride and SCH23390 needed to obtain a cataleptic response approximating that of either drug given alone. Thus, we may have used doses that by themselves do not produce either upregulation of DA receptors or behavioral supersensitivity. However, these doses are effective in blocking DA receptors as the catalepsy results indicate. On the other hand, it has been shown that blockade of one DA receptor subtype may attenuate the supersensitivity and upregulation associated with blockade of the other subtype (30). Similarly, we recently reported that behavioral supersensitivities produced by D_1 and D_2 DA antagonists are not additive (29). Thus, when SCH23390 and raclopride were coadministered these D_1/D_2 receptor interactions may also play a role inducing an equilibrium between both DA receptor subtypes that leads to a decrease of receptor upregulation and behavioral supersensitivity. Moreover, there is some evidence that the long-term administration of the D_1/D_2 mixed antagonist *cis*-flupenthixol not only enhances apomorphine-induced stereotyped behavior and D_2 receptor number but also increases DA-stimulated adenylate cyclase activity (27). This increase in cyclic adenosine monophosphate (cAMP) formation persisted for 6–12 months following the end of drug administration. It is thus conceivable that the effect on the D_1 DA system might be responsible for the rapid reversal of D_2 supersensitivity and the prevention of tolerance.

Combined D_1 and D_2 receptor blockade appears substantially more effective than either D_1 or D_2 receptor blockade alone in inducing catalepsy. This synergistic action allows doses of both compounds to be reduced and a decrease in DA agonist-induced stereotypy compared with the effects of either the D_1 or D_2 antagonists administered separately. Our results are not inconsistent with those reported previously. It has been demonstrated that mixed D_1/D_2 DA antagonists such as chlorpromazine produce behavioral supersensitivity to apomorphine after chronic treatment (7). However, these mixed antagonists induce a 65–85% occupancy of the D_2 receptor (12), while clozapine, which does not produce behavioral supersensitivity, induced a 40% D_2 occupancy and a 42% D_1 occupancy, suggesting that the behavioral supersensitivity observed with mixed antagonists reflects a higher occupancy of D_2 receptors.

Our findings could have clinical relevance. It has been observed that patients with extrapyramidal side effects induced by chronic neuroleptic administration tend to have higher occupancy of D_2 receptors than patients with no extrapyramidal symptoms (12). Use of selective D_1 and D_2 antagonists in combination might block DA receptors in equal proportion and thus diminish the risk of extrapyramidal side effects like tardive dyskinesia.

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