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The Actions of SCH 23390, a D1 Receptor Antagonist, on Operant and Avoidance Behavior in Rats

D. J. SANGER

Laboratoires d'Etudes et de Recherches Synthélabo (L.E.R.S)
31 av. P V. Couturier, 92220-Bagneux, France

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SANGER, D J *The actions of SCH 23390, a D1 receptor antagonist, on operant and avoidance behavior in rats* PHARMACOL BIOCHEM BEHAV 26(3) 509–513, 1987 —Previous studies have shown that dopamine antagonists such as haloperidol, pimozide and metoclopramide will produce gradually increasing decrements of operant and avoidance responding The present study was carried out to investigate whether the dopamine D1 blocking agent, SCH 23390, would exert a similar effect In the first experiment, SCH 23390 produced a dose-related (0 03–0 1 mg/kg) reduction in responding maintained by an FR 10 schedule of food reinforcement However, the compound gave rise to similar reductions of response rate throughout the 15 min session In a second experiment, higher doses of SCH 23390 (0 1–1 0 mg/kg) disrupted one-way avoidance performance in a shuttle-box Again, there was no within-session decline in responding after administration of SCH 23390 although injection of a dose of 0 4 mg/kg of haloperidol produced a greater response deficit during the second half of the session During 4 daily administrations of 0 3 mg/kg of SCH 23390 the degree to which avoidance responding was disrupted neither increased nor decreased SCH 23390 disrupts operant bar pressing and one-way avoidance responding but its actions in these behavioral tests are not identical to the effects of typical neuroleptics such as haloperidol

Operant responding Avoidance behavior D1 receptor Dopamine SCH 23390 Haloperidol

RECENTLY, SCH 23390 has been described as a selective antagonist at the D1 dopamine receptor subtype [11]. The pharmacological profile of this compound is similar to that of antipsychotic drugs such as haloperidol although a number of differences have also been identified [3, 8, 11].

In behavioral studies, SCH 23390 has been shown to reduce avoidance responding in rats and monkeys in doses lower than those which lead to the appearance of escape failures [8,11]. It also reduces locomotor activity [10] and decreases rates of responding maintained by electrical brain stimulation [12]. These are all effects characteristic of antipsychotic drugs It has also been shown, however, that the effects of neuroleptics on operant behavior are characterised by gradually developing rather than immediate reductions in responding. Thus, the rate-suppressing effects of drugs such as pimozide, haloperidol and metoclopramide increase gradually both within experimental sessions [5–7, 14] and across sessions when a drug is repeatedly administered [13,16]. The present study was carried out to investigate whether similar effects would be observed after administration of SCH 23390

METHOD

Subjects

Male, Wistar rats (Charles River, France), weighing 150–200 g when obtained from the supplier, were used. All animals were individually housed under standard laboratory conditions The rats used for studying food-reinforced operant responding were initially deprived of food for two days. They were subsequently given a standard quantity of chow each evening and water was always available in the home cages. Rats used in the study of avoidance behavior had food and water freely available in their home cages

Experiment 1

Nine rats were trained to bar press for food reinforcement in standard operant test chambers (Campden Instruments) as previously described [14]. These rats had served as subjects in the prevous study and had received injections of several other drugs before the investigation of SCH 23390 was carried out. A period of at least 14 days had elapsed since the previous drug treatment The animals responded on a fixed-ratio 10 (FR 10) schedule to obtain 45 mg food pellets (Bioserv) during daily 15 min sessions. Responses were recorded during the three successive five minute periods of each session

Experiment 2

Ten experimentally-naive rats were trained in a one-way shock avoidance task in a shuttle-box. The procedure was similar to that described previously [14] On each weekday the rats were given ten trials, separated by 30 sec inter-trial intervals. A rat was placed into the right-hand compartment of the box, in darkness with the guillotine door between the

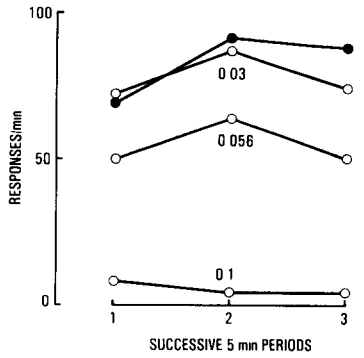

FIG 1 The effects of SCH 23390 on rates of bar pressing maintained by an FR 10 schedule of food reinforcement Response rates are presented for the three successive 5 min periods of the 15 min sessions Data were obtained from 9 rats which received all three doses in a mixed order The control values (filled circles) were obtained from three saline sessions Doses are in mg/kg

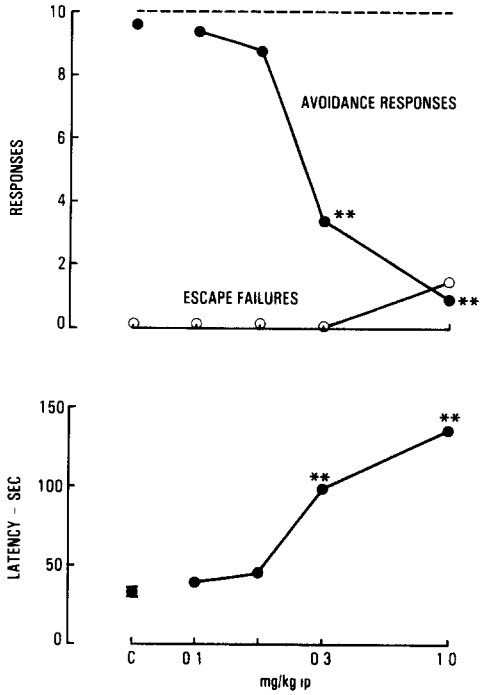

FIG 2 The effects of SCH 23390 on the avoidance performance of a group of 10 rats presented as the mean number of avoidance responses and failures to avoid and escape and the mean total response latency Each rat was given 10 trials each day and thus the maximum latency, had all failed to escape, was 200 sec $^{**}p<0$ 01 difference from control, Wilcoxon's test

two compartments closed Ten seconds later an overhead light was switched on and the guillotine door was removed. If the animal crossed the box during the next 10 sec an avoidance response was recorded If no response occurred, electric shock was applied through the grid floor (0 6 mA scrambled, Grason Stadler shocker 700) until the rat crossed the box (escape response) or for a maximum of 10 sec if no response occurred (escape failure). The animal remained in the left-hand compartment during the inter-trial interval after which it was replaced in the other compartment to commence the next trial. Responding was recorded as the number of avoidance and escape responses, the number of escape failures and the response latency These measures were recorded separately for the first and second halves of each daily session.

Drug Administration

Stable levels of responding were judged to have been established when day to day response rates of the operant-trained rats did not vary by a factor of more than 10 to 12% and when avoidance trained rats showed 9 or 10 successful avoidance responses every day. When such stable responding had been achieved the rats were injected with several doses of SCH 23390 injected 30 min before sessions The doses, chosen on the basis of preliminary experiments with other animals, were 0.03, 0.056 and 0.1 mg/kg for the rats trained to bar press for food and 0.1, 0.17, 0.3 and 1.0 mg/kg for the rats trained to avoid shock The drug was prepared in saline to which 2 drops of Tween 80/10 ml had been added and injected IP in volumes of 2 ml/kg. Drug injections were given on Tuesdays and Fridays and the different doses were given in a mixed order which was different for different rats Saline was injected on all intervening days and control data were obtained from Thursdays. The rats trained to avoid shock received, in addition to the four doses of SCH 23390, an injection of 0.4 mg/kg of haloperidol prepared in the same way as SCH 23390 and also injected IP. Finally, 10 days after the first part of the experiment, these same, avoidance-trained rats were divided into 2 groups to receive repeated injections of SCH 23390 or haloperidol. One rat died during this stage of the experiment. Five rats were given four daily injections of SCH 23390 at 0.3 mg/kg while the other four animals received four injections of 0 4 mg/kg of haloperidol

RESULTS

The effects of SCH 23390 on rates of bar pressing maintained by the FR 10 schedule are shown in Fig. 1 where the data are presented for the three successive five minute periods of the 15 min session. It is clear that SCH 23390 produced a dose-related decrease in rates of bar pressing, with responding being almost completely suppressed by the 0 1 mg/kg dose. The figure also indicates that the drug did not produce a within-session decline in responding during the three 5 min segments of the session. These response rate data were first analysed statistically using a Friedman two-way analysis of variance for overall response rates which showed a statistically significant effect of SCH 23390, $\chi r^2(3)=15.6$, $p<0$ 01 Further analysis with Wilcoxon matched pairs, signed ranks tests showed that only the highest dose (0 1 mg/kg) gave rise to a statistically significant decrease in response rate (T=0, N=9, $p<0.01$) Wilcoxon tests comparing the data for the first and third 5 min periods for each dose of SCH 23390 showed that in no case was the number of responses in the third period significanly less than that in the first period although under control conditions there was a statistically significant increase in responding between the first and third periods (T=0, N=9, $p<0.01$)

Figure 2 presents the effects of SCH 23390 on avoidance responding in terms of the mean numbers of avoidance re-

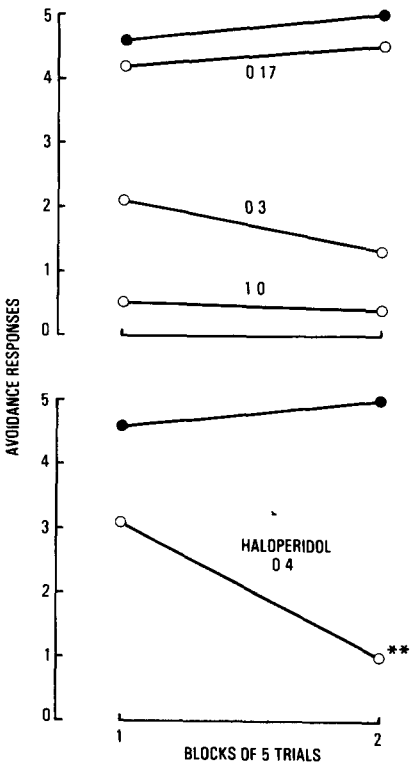

FIG 3 The effects of SCH 23390 and haloperidol on the mean number of avoidance responses shown separately for the two blocks of 5 trials of the 10 trial sessions SCH 23390 produced similar decreases from the control values (filled circles) whereas haloperidol produced a greater effect during the second half of the session Doses are in mg/kg **$p<0$ 01 difference between the first and second block of 5 trials, Wilcoxon's test

sponses and escape failures and the mean total response latency for the 10 trials. SCH 23390 produced a dose-related disruption of avoidance responding although escape failures began to occur only at the dose of 1.0 mg/kg. Statistically significant (Wilcoxon's test) decreases in numbers of responses were produced by 0.3 mg/kg (T=0, N=9, $p<0.01$) and 1.0 mg/kg (T=0, N=10, $p<0.01$). Similarly, response latencies were significantly increased by 0.3 mg/kg (T=0, N=10, $p<0$ 01) and 1.0 mg/kg (T=0, N=10, $p<0.01$). The lower doses (0.1 and 0.17 mg/kg) did not produce statistically significant effects

The effects of SCH 23390 on avoidance responses are also presented in Fig. 3 which shows these responses for the two blocks of 5 trials. SCH 23390 produced approximately similar disruptions of responding during the first and second halves of the 10 trial sessions. In contrast, the dose of haloperidol tested in the same rats gave rise to a greater disruption of avoidance responding during the second half of the session. As shown in Fig. 3, there was a statistically significant decrease in the number of avoidance responses from the first to the second half of the session after haloperidol injection (T=0, N=8, $p<0.01$, Wilcoxon's test) No statistically significant changes between the two 5 trial blocks were seen after injection of saline or SCH 23390

Table 1 shows the effects of four, repeated administrations of SCH 23390 (0 3 mg/kg) or haloperidol (0 4 mg/kg) on avoidance behavior. Although these data are limited because of the small number of animals involved, it is clear that no tolerance occurred to the effects of either compound. In fact, in terms of escape failures and response latency, the effects of haloperidol appeared to be slightly greater after the third and fourth administration than after the first and second injections. Because of the small numbers of animals in each condition, these data were not subjected to statistical analysis

TABLE 1

EFFECTS OF REPEATED ADMINISTRATION OF SCH 23390 (0 3 mg/kg) AND HALOPERIDOL (0 4 mg/kg) ON ONE-WAY AVOIDANCE RESPONDING IN RATS

			Drug Days			
Condition	Measure	Control	1	2	3	4
SCH 23390 0 3 mg/kg n=5	Avoidance Responses	9 6 ± 0.2	2 4 ± 1 7	2 4 ± 1 3	4 4 ± 1 6	3 2 ± 1 6
	Escape Failures	0	0 2 ± 0 2	0	0 4 ± 0 4	0 4 ± 0 4
	Response Latency	27 ± 5	107 ± 22	101 ± 14	87 ± 22	97 ± 22
Haloperidol 0 4 mg/kg n=4	Avoidance Responses	8 3 ± 0 2	2 5 ± 0 6	3 5 ± 1 6	3 0 ± 2 0	1 3 ± 1 1
	Escape Failures	0	0	0 5 ± 0 4	2 5 ± 1 8	1 8 ± 0 9
	Response Latency	42 ± 3	99 ± 6	93 ± 19	117 ± 28	130 ± 19

Each value is the mean number (±SEM) of avoidance responses, escape failures or response latency/session in seconds for the sessions of 10 trials

DISCUSSION

The present results show that the D1 receptor antagonist SCH 23390 produced dose-related disruptions of operant bar pressing and one-way shock avoidance performance These results are thus consistent with previous studies showing that this compound reduces shock avoidance responding, locomotor activity and responding maintained by electrical stimulation of the brain [10–12]. It is notable that in the present study there was a wide separation between the doses of SCH 23390 which reduced rates of food-reinforced lever pressing and those which disrupted avoidance performance Previous studies have shown that one-way avoidance responding is less sensitive to disruption by a variety of drugs than is bar pressing [14] However, the approximately 10 fold difference in doses of SCH 23390 active in the two procedures is a separation greater than that seen with other dopamine antagonists and neuroleptics although this difference may be related to the differential previous experience of the animals used in the two experiments It is also interesting to note that in a previous study [11], the avoidance responding of rats was disrupted by SC injections of SCH 23390 at doses considerably lower than those which were active in the present experiment. It is not clear, however, whether this difference is related to procedural differences or the different routes of drug administration

The major purpose of the present study was to investigate whether SCH 23390 would give rise to within-session response decrement patterns similar to those seen previously with pimozide, haloperidol and metoclopramide It did not In both experiments active doses of SCH 23390 produced approximately similar disruptions of responding during early and later parts of experimental sessions Although the lack of a within-session decline in operant responding after SCH 23390 might be related to the fact that the animals used in this experiment had previously received injections of several other drugs, this was not the case for the avoidance trained rats In a previous study, using similar methods, haloperidol and metoclopramide produced within-session response decrement patterns of both operant and avoidance responding although the atypical antipsychotic, clozapine, and several drugs from other categories did not [14]

One possible explanation of the failure of SCH 23390 to produce the within-session response decrements seen with other dopamine antagonists is that this effect is associated with antagonism at D2 rather than at D1 receptors. Whether this observation has any relevance for the potential use of D1 antagonists as antipsychotic drugs is uncertain However, as the within-session decline in responding is not produced by clozapine [14], an effective antipsychotic which produces few extrapyramidal side-effects, it would seem likely that this phenomenon is associated with the motor side-effects rather than with the therapeutic action of drugs such as haloperidol It is also interesting to note that, in a recent paper [1], it was shown that clozapine and other atypical antipsychotic drugs were quite potent inhibitors of [^{3}H]SCH 23390 binding in mouse brain The authors of this paper speculated that their results might indicate the involvement of D1 receptors in the therapeutic effect of atypical antipsychotics

Four daily injections of SCH 23390 were administered to the avoidance trained rats because, in a previous study [13], it was found that a similar number of injections of haloperidol (0 2 mg/kg) produced a gradually increasing disruption of avoidance responding in a different test In contrast, complete tolerance developed to the effect of clozapine (20 mg/kg) on avoidance behavior after four daily injections with an appreciable degree of tolerance being apparent by the second day Other studies also have reported rapidly developing tolerance to the behavioral effects of clozapine [4,15] and an increasing effect of haloperidol and similar drugs with repeated administration [2,9] In the present experiment, repeated injections were given of SCH 23390 at 0 3 mg/kg and haloperidol at 0 4 mg/kg These were doses which produced similar disruptions of avoidance behavior on acute administration Although the present data on repeated administration are limited, they indicate that, in the avoidance procedure used here, there was also a tendency for the effect of haloperidol to be greater after the third and fourth than after the first and second injections. The effects of SCH 23390 were similar during the four daily administrations indicating that this compound, at the dose used, neither gave rise to a haloperidol-like accumulating effect nor produced tolerance similar to that seen with clozapine

In summary, the present results show that while SCH 23390 disrupts both operant and avoidance behavior in rats, these effects are not identical to those produced by neuroleptic drugs such as haloperidol These results are thus consistent with those of previous studies in which differences between the pharmacological effects of SCH 23390 and those of dopamine antagonists not selective for the D1 receptor were described [3, 8, 11]

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