Pharmacology Biochemistry and Behavior, Vol. 41, pp. 507–510, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Dopamine D_1 Antagonists Potentiate the Durations of Bar and Cling Catalepsy and the Dorsal Immobility Response in Rats

MERLE E. MEYER,[1] GEORGIA A. COTTRELL AND CAROL VAN HARTESVELDT

Department of Psychology and Center for Neurobiological Sciences, University of Florida, Gainesville, FL 32611

Received 2 October 1991

MEYER, M. E., G. A. COTTRELL AND C. VAN HARTESVELDT. *Dopamine D_1 antagonists potentiate the durations of bar and cling catalepsy and the dorsal immobility response in rats.* PHARMACOL BIOCHEM BEHAV 41(3) 507–510, 1992.—The effects of dopamine D_1 antagonists SCH 23390 or SK&F 83566 (at SC doses of 0.00, 0.01, 0.05, and 0.1 mg/kg) were tested for 2 h on bar and cling catalepsy and the dorsal immobility response. Each of the drugs potentiated the duration of each of the three measures of immobility in a dose- and time-dependent manner. Each of the drugs had rapid but brief effects on all three response measures; the peak effect of SK&F 83566 took place at 20 min and that for SCH 23390 at 40 min for each behavior. At each effective drug dose, SCH 23390 had a greater effect than SK&F 83566 on each behavior. Dopamine D_1 antagonists potentiated three different immobility responses, as do dopamine D_2 antagonists.

Dopamine D_1 antagonist Immobility SCH 23390 SK&F 83566 Rats

DOPAMINE D_1 and D_2 agonists administered systemically have different behavioral effects. D_2 agonists enhance locomotion (2), while D_1 agonists induce grooming (6) and abnormal oral movements (10). On the other hand, both dopamine D_1 and D_2 antagonists induce immobility responses such as bar and vertical cling catalepsy (3,7,9,12), although the time courses of the D_1 and D_2 antagonists are different (7,9).

Another type of immobility response is the dorsal immobility response (DIR), which is different from the bar and vertical cling catalepsy in that the DIR can be elicited in undrugged animals and does not have grasping as a major response component. The DIR is a species-typical response experimentally elicited by grasping an animal by the dorsal skin at the nape of the neck and lifting the animal off its feet so that the animal is not in contact with any other surface. In the rat, the animal immediately exhibits a stereotypical immobility response that persists for a period of time until the animal emits escape-like behaviors. In the untreated rat, the duration of the DIR approximates 45–90 s (11,13). Haloperidol, primarily a dopamine D_2 antagonist, greatly potentiates the duration of the DIR (3).

One purpose of the present experiments was to ascertain whether dopamine D_1 antagonists such as SCH 23390 would also potentiate the DIR and, if so, to compare the time course and dose-response curves for their effects on the DIR with those for the bar and vertical cling catalepsy. A second purpose of these experiments was to determine the generality of the effects of two structurally similar dopamine D_1 antagonists, SCH 23390 and SK&F 83566, on all three immobility response measures. While SCH 23390 potentiates bar and vertical cling catalepsy, and SK&F 83566 has proven effective in blocking locomotor and sniffing induced by apomorphine (4,5,8), the capacity of SK&F 83566 to induce immobility responses has not been assessed.

METHOD

Animals

Long-Evans hooded male rats, weighing between 220–300 g, were obtained from Charles River. They were housed individually, had food and water ad lib, and were maintained on a 12 L:12 D (0800–2000) cycle. Animals were tested in the light phase between 1300–1600 h. This study was carried out in compliance with the rules set forth in the *NIMH Guide for the Care and Use of Laboratory Animals.*

Drugs

SCH 23390 [*R*-(+)-7-chloro-8-hydroxy-3-methyl-1phenyl-2,3,4,5-tetrahydro-1-*H*-3-benzazapine hydrochloride] (Schering) and SK&F 83566 [(±)-7-bromo-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1-*H*-3-benzazapine hydrochloride] (Smith, Kline & French) were each dissolved in distilled water. The drugs were obtained from Research Biochemicals Incorporated (Natick, MA).

[1] Requests for reprints should be addressed to Merle E. Meyer, Department of Psychology, University of Florida, Gainesville, FL 32611.

Experimental Procedures

Drugs were administered SC in a volume of 0.1 ml/kg. Dosages used for both SCH 23390 and SK&F 83566 were 0.00 (vehicle control), 0.01, 0.05, and 0.1 mg/kg. There were 10 animals in each drug dose group.

Following SC injection, animals were behaviorally tested at 5, 20, 35, 60, and 120 min postinjection. At the time of testing, the rat was removed from the home cage and placed within a V-shaped trough for 30 s. At each time point, the animal was tested on a single trial for bar catalepsy, vertical cling catalepsy, and the DIR, with a 30-s interresponse time interval in the trough. The order of behavioral testing at each time point and for each animal was random. The experimenter was unaware of the drug or the dosage; thus, animals were tested blind.

Response Measurements

Measurement of bar catalepsy. The animal was held by its back and shoulders and moved forward to the bar with the hind legs contacting the table top; the animal's two forepaws were placed on a 0.5-cm diameter horizontal stainless steel bar 8 cm high to the table. The measurement for bar catalepsy was the duration from releasing of the hand support, once the animal grasped the bar, until the animal placed both forepaws on the table or until 120 s had elapsed.

Measurement of vertical cling catalepsy. The animal was placed in a head-up position on a 90° vertical grid (standard hardware cloth with 8 wires per 10 cm) 30 cm above a table with the animal's forepaws separated by at least 0.5 cm. When the animal grasped the wire grid, it became self-supporting. Vertical cling catalepsy was measured from the time of the hand release until the animal moved a paw to a different position or until 120 s had elapsed.

Measurement of DIR. To induce the DIR, the animal was gently grasped by the dorsal skin at the nape of the neck and lifted off its feet with no other part of the animal's body touching any other surfaces. As all rats elicit the species-typical immobility response when the DIR was first induced, the duration was measured from the onset of the DIR until the animal emitted directed movements associated with escape-like behaviors or until 300 s had elapsed.

Statistics

Each treatment group consisted of 10 rats chosen at random. A two-factor mixed design analysis of variance (ANOVA) was applied to each drug and for each of the three immobility measures and was used to examine the effects of the treatment conditions upon the duration of immobility over the time course. Significant interactions for the dose by time interval were followed up by treatment by block (repeated measures or within treatment) ANOVA's. Duncan's multiple range test was used for making subsequent pairwise comparisons between groups, and p values equal to or less than 0.05 were judged statistically significant.

RESULTS

Effects of SCH 23390

As shown in Figs. 1A, 1B, and 1C, SCH 23390 potentiated the duration of all three measures in a dose- and time-dependent manner. For the bar catalepsy shown in Fig. 1A, there were highly significant effects of dose, $F(3,36) = 10.68$, $p < 0.001$, time course, $F(4,144) = 12.25$, $p < 0.001$, and a dose by time course interaction, $F(12,144) = 5.95$, $p < 0.001$. At each of the time intervals from 5 min through 60 min, the 0.1-mg/kg group had significantly longer durations than all other groups (p's < 0.01); all other groups did not differ from one another (p's > 0.05). There were

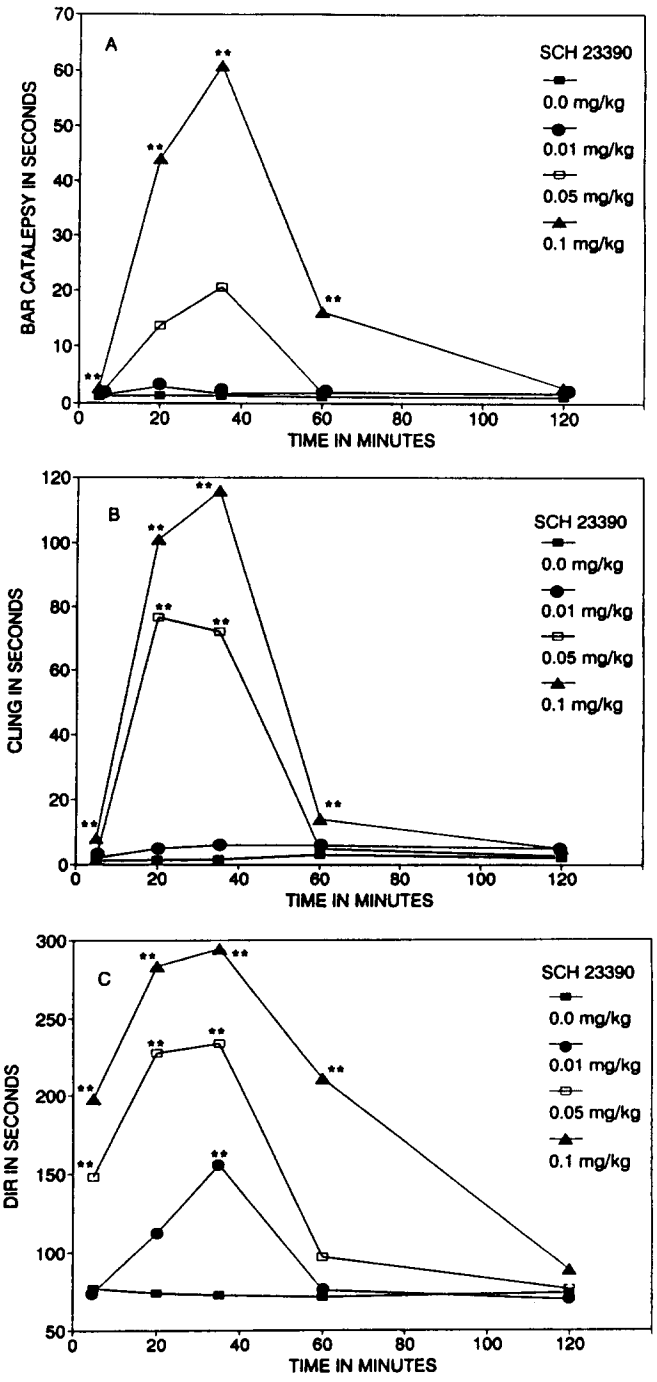

FIG. 1. Effects of several doses of the dopamine D-1 antagonist SCH 23390 on three measures of immobility in the rat. (A) Duration of bar catalepsy. (B) Duration of vertical cling catalepsy. (C) Duration of the DIR. Significant differences from the vehicle control group (0.00 mg/kg) at each time point: $^{**}p < 0.01$.

no significant differences among groups at 120 min (p's > 0.05).

For the vertical cling catalepsy shown in Fig. 1B, there were highly significant effects of dose, $F(3,36) = 55.88$, $p < 0.001$, time course, $F(4,144) = 101.82$, $p < 0.001$, and the dose by time interaction, $F(12,144) = 35.69$, $p < 0.001$. At 5 min, the 0.1-mg/kg group had significantly longer durations than all other groups (p's < 0.01); all other groups did not differ significantly from one another. At 20 min, both the 0.1- and 0.05-mg/kg groups had significantly longer durations than the 0.01- and 0.00-mg/kg groups (p's < 0.01) and differed significantly from one another ($p < 0.05$); the 0.01-mg/kg group did not differ significantly from the vehicle control group. At 35 min, all groups differed significantly from one another (p's < 0.01) except the 0.01- and 0.00-mg/kg groups. At 60 min, the 0.1-mg/kg group had significantly longer durations than all other groups (p's < 0.01); all other groups did not differ significantly from one another (p's > 0.05). There were no significant differences at 120 min (p's > 0.05).

For the DIR shown in Fig. 1C, there were highly significant effects of dose, $F(3,36) = 35.18$, $p < 0.001$, time course, $F(4,144) = 67.56$, $p < 0.001$, and dose by time course interaction, $F(12,144) = 13.55$, $p < 0.001$. At 5 and 20 min, both the 0.05- and 0.1-mg/kg groups differed significantly from the other two groups (p's < 0.01) and from each other ($p < 0.05$), while the 0.01-mg/kg and the vehicle control groups did not differ significantly. At 35 min, all dose groups differed significantly from one another (p's < 0.01). At 60 min, the 0.1-mg/kg group had significantly longer durations than all other groups (p's < 0.01), while all other groups did not differ significantly from one another (p's > 0.05). There were no significant differences between the groups at 120 min ($p > 0.05$).

Effects of SK&F 83566

As shown in Figs. 2A, 2B, and 2C, SK&F 83566 potentiated the durations of all three measures in a dose- and time-dependent manner. For the bar catalepsy shown in Fig. 2A, there were highly significant effects of dose, $F(3,36) = 11.98$, $p < 0.001$, time course, $F(4,144) = 22.50$, $p < 0.001$, and the dose by time course interaction, $F(12,144) = 9.39$, $p < 0.001$. Only the highest dose, 0.1 mg/kg, significantly increased the duration of bar catalepsy at the 5-min interval and had longer durations than all other groups (p's < 0.01). At 20 min, the 0.1-mg/kg group had significantly greater scores than the 0.05-mg/kg group ($p < 0.05$) and the 0.01-mg/kg and vehicle groups (p's <0.01); the 0.5-mg/kg group also had significantly higher scores than the 0.01-mg/kg and vehicle groups (p's < 0.05). At 35 min, the 0.1-mg/kg group had significantly higher scores ($p < 0.01$) than all other groups, which did not differ significantly from one another ($p > 0.05$). At 60 and 120 min, there were no significant differences.

For the cling catalepsy shown in Fig. 2B, there were highly significant dose effects, $F(3,36) = 8.16$, $p < 0.001$, time course, $F(4,144) = 8.07$, $p < 0.001$, and dose by time course interaction, $F(12,144) = 4.69$, $p < 0.001$. At 5, 20, and 35 min, the 0.1-mg/kg group had significantly longer durations than all other groups (p's < 0.01); no other group differed significantly from any other group (p's > 0.05). There were no significant group differences at 60 or 120 min.

For the DIR shown in Fig. 2C, there were highly significant dose effects, $F(3,36) = 27.16$, $p < 0.001$, time course, $F(4,144) = 155.84$, $p < 0.001$, and dose by time course interaction, $F(12,144) = 75.37$, $p < 0.001$. At 5 min, there were no significant differences among the groups; at 20 min, all groups differed significantly from one another (p's < 0.01) except the 0.01-mg/kg and the vehicle groups. At 35 min, the 0.1-mg/kg group had significantly longer durations than those of the 0.05- and 0.01-mg/kg groups (p's < 0.05), as well as

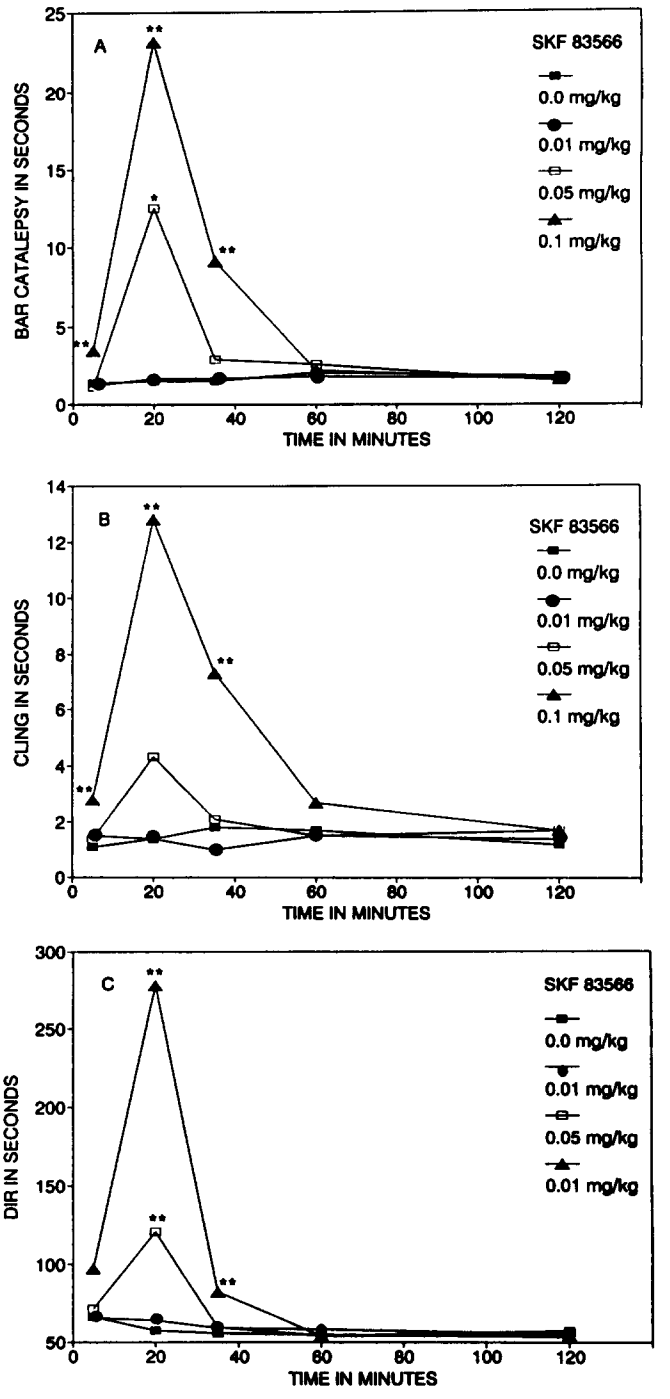

FIG. 2. Effects of several doses of the dopamine D-1 antagonist SK&F 83566 on three measures of immobility in the rat. (A) Duration of bar catalepsy. (B) Duration of vertical cling catalepsy. (C) Duration of the DIR. Significant differences from the vehicle control group (0.00 mg/kg) at each time point: *$p < 0.05$, **$p < 0.01$.

those of the vehicle group ($p < 0.01$); no other comparisons were significant. There were no significant differences among the groups at 60 or 120 min.

DISCUSSION

The results of the present experiments replicate and extend the findings of the prior studies of the effects of dopamine D_1 antagonists on immobility responses. Consistent with previous results, SCH 23390 enhanced both bar catalepsy (12) and vertical cling catalepsy (9) in a dose-dependent manner with a rapid onset and offset. Furthermore, SCH 23390 also potentiated the duration of the DIR with a virtually identical time course. The potentiation of the durations of all three measures of immobility was apparent 5 min following the systemic injection of SCH 23390, with a time of peak effect at 35 min and a duration of approximately 1 h. Therefore, despite the differences in the methods of eliciting these three responses, as well as the differences in the response topographies, SCH 23390 potentiated the duration of all of them. The DIR proved the most sensitive of the three measures in that the lowest dose level of SCH 23390 used in this study had a significant effect on this response, but this lowest dose did not affect the two measures of catalepsy.

The second dopamine D_1 antagonist, SK&F 83566, also potentiated the durations of all three immobility responses similar to the potentiation of SCH 23390. As with SCH 23390, the onset of the SK&F 83566 effect was rapid. However, the peak effect was sooner at 20 min and the duration of the effect was shorter (less than 60 min) than the SCH 23390 effects. The peak effect of SK&F 83566 on each behavior was far less than that of SCH 23390. At the largest dose used in this study, the effects on the duration by SK&F 83566 were only half of that of SCH 23390 on bar catalepsy and only one tenth its effect on the vertical cling catalepsy. For the DIR, the peak effects of the largest drug doses for the two D_1 antagonists were similar, probably due to a "ceiling effect"; however, at the medium dose SK&F 83566 had only about half the effect of SCH 23390. In previous research in which SCH 23390 and SK&F 83566 in a similar dose range were used to block apomorphine-induced stereotyped behavior, differences in the effectiveness of the two drugs were not discernible (4,5). As SCH 23390 and SK&F 83566 are structurally similar compounds that bind to dopamine D_1 receptors, with their difference being only in the halide substitution at position 7 of the benzazepine structure, it was important to ascertain any differences using an immobility paradigm rather than an activation one.

Despite differences between dopamine D_1 and D_2 receptors with respect to adenylate cyclase, and despite differences in the distribution of the receptors in various brain regions (1), the D_1 and D_2 antagonists potentiate the duration of three disparate immobility behaviors. Further research is necessary to determine whether the full spectrum of D_2 antagonist effects is also found for the D_1 antagonists.

ACKNOWLEDGEMENTS

The authors thank Bonnie McLaurin for excellent technical assistance and Jeanene Griffin for secretarial assistance. This research was supported by a Whitehall Foundation grant to M.E.M.

REFERENCES

1. Camps, M.; Kelly, P. H.; Palacios, J. M. Autoradiographic localization of dopamine D1 and D2 receptors in the brain of several mammalian species. J. Neural Transm. 80:105–127; 1990.
2. Eilam, D.; Szechtman, H. Biphasic effect of D-2 agonist quinpirole on locomotor and movements. Eur. J. Pharmacol. 161:151–157; 1989.
3. Meyer, M. E.; Smith, R. L.; Van Hartesveldt, C. Haloperidol differentially potentiates tonic immobility, the dorsal immobility response and catalepsy in the developing rat. Dev. Psychobiol. 17:383–389; 1984.
4. Molloy, A. G.; O'Boyle, K. M.; Pugh, M. T.; Waddington, J. L. Locomotor behaviors in response to new selective D-1 and D-2 dopamine receptor agonists, and the influence of selective antagonists. Pharmacol. Biochem. Behav. 25:249–253; 1986.
5. Molloy, A. G.; Waddington, J. L. The enantiomers of SK&F 83566, a new selective D-1 dopamine antagonist, stereospecifically block stereotyped behaviour induced by apomorphine and by the selective D-2 agonist RU 24213. Eur. J. Pharmacol. 116: 183–186; 1985.
6. Molloy, A. G.; Waddington, J. L. Assessment of grooming and other behavioural responses to the D-1 dopamine receptor agonist SK&F 38393 and its R- and S-enantiomers in the intact adult rat. Psychopharmacology (Berl.) 92:164–168; 1987.
7. Morelli, M.; Di Chiara, G. Catalepsy induced by SCH 23390 in rats. Eur. J. Pharmacol. 117:179–185; 1985.
8. O'Boyle, K. M.; Waddington, J. L. Identification of the enantiomers of SK&F 83566 as specific and stereoselective antagonists at the striatal D-1 receptor: Comparisons with the D-2 enantioselectivity of Ro22-1319. Eur. J. Pharmacol. 106:219–220; 1984.
9. Ogren, S. O.; Fuxe, K. D1- and D2-receptor antagonists induce catalepsy via different efferent pathways. Neurosci. Lett. 85:333–338; 1988.
10. Rosengarten, H.; Schweitzer, J. W.; Friedhoff, A. J. Induction of oral dyskinesia in naive rats by D-1 stimulation. Life Sci. 33: 2479–2482; 1983.
11. Smith, R. L.; Meyer, M. E. Morphine and naloxone effects on tonic immobility and the dorsal immobility response in the adult rat. Pharmacol. Biochem. Behav. 22:505–507; 1985.
12. Undie, A. S.; Friedman, E. Differences in cataleptogenic actions of SCH 23390 and selected classical neuroleptics. Psychopharmacology (Berl.) 96:311–316; 1988.
13. Webster, D. G.; Lanthorn, T. H.; Dewsbury, D. A.; Meyer, M. E. Tonic immobility and the dorsal immobility response in twelve species of muroid rodents. Behav. Neural Biol. 31:32–41; 1981.