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Effects of Dopamine D_1 Antagonists SCH23390 and SK&F83566 on Locomotor Activities in Rats

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MEYER, M. E., G. A. COTTRELL, C. VAN HARTESVELDT AND T. J. POTTER. *Effects of dopamine D_1 antagonists SCH23390 and SK&F83566 on locomotor activities in rats.* PHARMACOL BIOCHEM BEHAV **44**(2) 429–432, 1993.—The effects of the dopamine D_1 antagonists *R*-(+)-7-chloro-8-hydroxy-3-methyl-1phenyl-2,3,4,5-tetrahydro-1-*H*-3-benzazapine (SCH23390) and (±)-7-bromo-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1-*H*-3-benzazapine (SK&F83566) were tested for 2 h on linear locomotor, rearing, stereotypy, and margin times in an open field. Each of the antagonists attenuated the duration of linear locomotion, rearing, and stereotypy times in a dose- and time-dependent manner. The effectiveness of the antagonists was relatively brief and SCH23390 was more effective than SK&F83566 on each behavior. The two antagonists had differential effects on margin time.

Dopamine D_1 antagonist Linear locomotion Rearing Stereotypy Thigmotaxis
SCH23390 SK&F83566 Rats

THE dopamine receptors are currently classified as either D_1 or D_2 receptor subtypes, where the D_1 receptor activates adenylate cyclase and the D_2 receptor is either independent of adenylate cyclase or mediates its inhibition (10,16). The availability of agonists and antagonists acting primarily at the D_1 or D_2 receptor sites has stimulated research to characterize the functional effects of each receptor subtype. Selective D_1 antagonists have been developed, including *R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1-*H*-3-benzazapine (SCH23390) (7–9) and a related derivative, (±)-7-bromo-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1-*H*-3-benzazapine (SK&F83566) (1,12,13). It has been suggested that both the D_1 and D_2 receptors must be stimulated to achieve the full range of dopamine-induced behaviors. However, of particular interest has been the effectiveness of SCH23390 and SK&F83566 in blocking various behaviors induced by D_1, D_2, and mixed D_1/D_2 agonists (2–4,18).

Relatively little research has centered on inhibitory effects of D_1 antagonists upon various locomotor activities. SCH23390 has been reported to inhibit motor activities in mice (15) and reduce horizontal activity (5,6) and rearing (6) in a repeated dose-dependent manner in rats. However, repeated administration of SCH23390 enhances locomotor activity (14,17).

The primary function of the present experiments was to replicate the effects of SCH23390 on various locomotor behaviors and compare the time course and dose-response curves. A secondary function was to determine the generality of the effects of two structurally similar dopamine D_1 antagonists, SCH23390 and SK&F83566, on various locomotor activities. While SCH23390 may inhibit horizontal and rearing activities, the effectiveness of SK&F83566 has not been assessed.

METHOD

Animals

Male Long-Evans rats weighing 200–225 g were obtained from Charles River. The rats were individually housed in stainless steel cages, had food and water ad lib, and were maintained on a 12 L : 12 D (0700–1900 h) light cycle. Animals were tested in the light phase between 1000–1600 h. The room in which animals were maintained was at a constant temperature (21 ± 2°C). This study was carried out in compliance with the rules set forth in the *NIH Guide for the Care and Use of Laboratory Animals.*

Drugs

SCH23390 HCl (Schering, Kenilworth, NJ) and SK&F83566 HCl (Smith, Kline & French, Philadelphia, PA)

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were each dissolved in distilled water. Drugs were administered SC in the volume of 0.1 ml/kg. The dosages used for SCH23390 were 0.00 (vehicle control), 0.01, 0.05, 0.1, and 0.2 mg/kg and for SK&F83566, 0.00, 0.01, 0.1, and 1.0 mg/kg. The drugs were obtained from Research Biochemicals Inc. (Natick, MA).

Apparatus

Immediately following SC drug administration, each rat was placed in an Omnitech Digiscan Animal Activity Monitor (Omnitech Electronics, Columbus, OH) for 120 min. In the two experiments, data were collected every 10 min. The acrylic cage within the monitor measured approximately 42 × 42 × 30.5 cm. The monitor was equipped with 16 beams 2.54 cm apart from front to back and from side to side. The Digiscan analyzer converted the patterns of the beams broken into different measures of locomotor activity. The measures analyzed (in seconds) in this study were the total linear time the animal moved, rearing time, stereotypy time, and margin time.

Statistics

Ten rats were randomly assigned for each independent dose level. Each rat was tested only once. A two-factor mixed-design analysis of variance (ANOVA) was used to analyze the within measures (six 10-min time blocks), between the drug treatment conditions, and the time block × dose interaction effect. Significant interactions for the dose × time interval were followed up with the Dunnett's multiple-comparison tests between the control group and treatment groups at each time block. p values equal to or less than 0.05 were judged statistically significant.

RESULTS

Locomotor Effects of SCH23390

Figure 1 illustrates the 120-min time course of linear locomotor, rearing, stereotypy, and margin times of rats (measured in seconds) treated with one of five dose levels of SCH23390 (0.00 or vehicle, 0.01, 0.05, 0.1, or 0.2 mg/kg).

Linear locomotor time. ANOVA revealed a significant dose effect, $F(4, 45) = 26.61$, $p < 0.001$; time block effect, $F(11, 495) = 152.93$, $p < 0.001$; and dose × time block interaction, $F(44, 495) = 19.34$, $p < 0.001$. The dosages of 0.05, 0.1, and 0.2 mg/kg significantly attenuated linear locomotion at each time block from 10–40 min ($p < 0.01$). On the other hand, the dose level of 0.01 mg/kg significantly potentiated locomotion at time blocks 10, 40, and 50 min ($p < 0.01$).

Rearing time. ANOVA showed a significant dose effect, $F(4, 45) = 24.60$, $p < 0.001$; time block effect, $F(11, 495) = 46.90$, $p < 0.001$; and dose × time block interaction, $F(44, 495) = 9.91$, $p < 0.001$. Rearing time emitted by the 0.05-, 0.1-, and 0.2-mg/kg groups was significantly suppressed between the time block intervals of 10–60 min; however, at 30 min the 0.01-mg/kg group emitted significantly more rearing time than their comparable controls.

Stereotypy time. ANOVA indicated a significant dose effect, $F(4, 45) = 17.32$, $p < 0.001$; time effect, $F(11, 495) = 30.35$, $p < 0.001$; and dose × time block interaction, $F(44, 495) = 5.65$, $p < 0.001$. The 0.05-, 0.1-, and 0.2-mg/kg groups emitted significantly less stereotypy time between 10–40 min and the 0.1- and 0.2-mg/kg groups at 60 min.

Margin time. ANOVA resulted in a significant dose effect, $F(4, 45) = 7.82$, $p < 0.001$; time course effect, $F(11, 495) = 33.10$, $p < 0.001$; and dose × time course interaction, $F(44,$

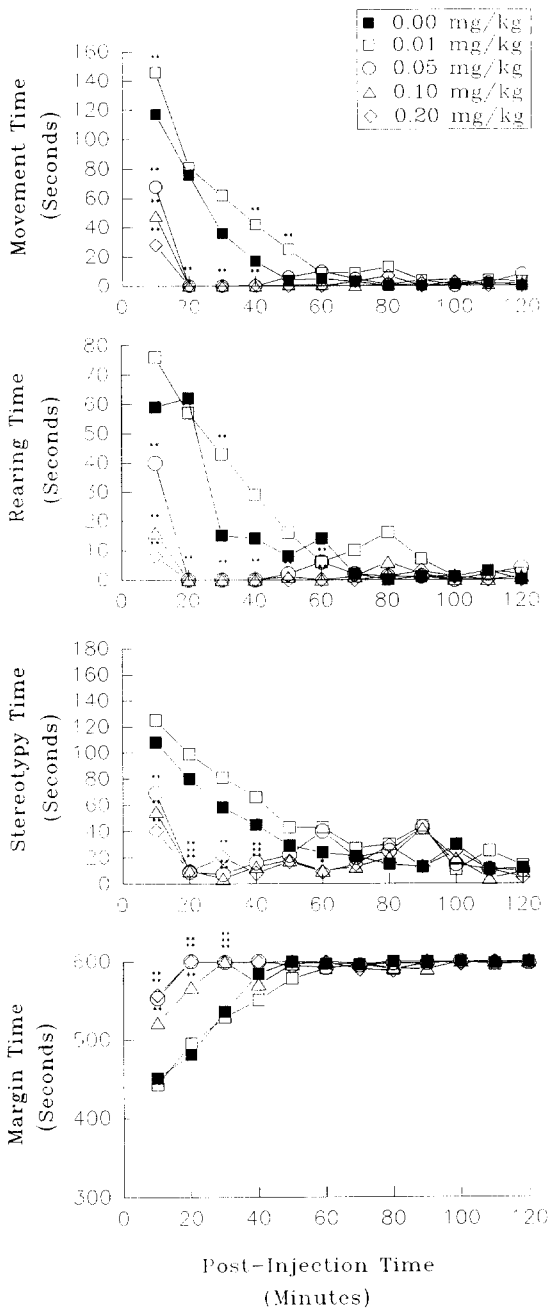

FIG. 1. Effects of several dosages of the dopamine D_1 antagonist SCH23390 on four measures of locomotor activity (in seconds) over 120 min: Horizontal movement, rearing, stereotypy, and margin times. Significant differences from the vehicle control group (0.00 mg/kg) at each time point: $*p < 0.05$, $**p < 0.01$. For clarity, the error bars have not been included.

495) = 4.37, $p < 0.001$. Animals in the 0.05-, 0.1-, and 0.2-mg/kg groups emitted significantly more margin time or thigmotaxis during the 10- through 30-min time course ($p < 0.01$).

Locomotor Effects of SK&F83566

Figure 2 illustrates the 120-min time course of linear locomotor, rearing, stereotypy, and margin times of rats (measured in seconds) treated with one of four dose levels of SK&F83566 (0.00 or vehicle, 0.01, 0.1, or 1.0 mg/kg).

Linear locomotor time. ANOVA demonstrated a significant dose effect, $F(3, 26) = 15.32$, $p < 0.001$; time course effect, $F(11, 286) = 116.39$, $p < 0.001$; and dose × time course interaction, $F(33, 286) = 7.60$, $p < 0.001$. The 0.1-mg/kg group suppressed locomotor activity time at the 20- and 30-min time blocks, whereas the 1.0-mg/kg group locomotor time was attenuated during the 60 min following injection. At time block 20 min, 0.01 mg/kg potentiated this behavior.

Rearing time. ANOVA showed a significant dose effect, $F(3, 26) = 7.21$, $p < 0.001$; time course effect, $F(11, 286) = 32.27$, $p < 0.001$; and dose × time course interaction, $F(33, 286) = 4.23$, $p < 0.001$. At 20 and 30 min, 0.1 mg/kg inhibited rearing time. On the other hand, 1.0 mg/kg suppressed rearing during the first 60 min.

Stereotypy time. ANOVA resulted in a significant dose effect, $F(3, 26) = 16.02$, $p < 0.001$; time course effect, $F(11, 286) = 24.75$, $p < 0.001$; and dose × time course interaction, $F(33, 286) = 3.28$, $p < 0.001$. The 0.1-mg/kg dose suppressed stereotypy time in time blocks of 20 and 30 min and the 1.0-mg/kg dose suppressed this behavior from 10–60 min.

Margin time. ANOVA revealed a significant dose effect, $F(3, 26) = 3.32$, $p < 0.05$; and a significant time course effect, $F(11, 286) = 5.18$, $p < 0.001$; whereas the dose × time course interaction was not significant ($p > 0.05$). During the 10- through 60-min period, 1.0 mg/kg significantly attenuated margin time or thigmotaxis.

DISCUSSION

Prior research on the effects of the dopamine D_1 antagonist SCH23390 on locomotor behavior reported an inhibition of behaviors as a function of various dose levels (5,6,15) in both mice and rats but the effectiveness of SCH23390 on locomotor behaviors over a time course has not. In addition, the results may be confounded by the repeated testing of the same subjects with SCH23390 (5,6,14,17).

The present study has shown that SCH23390 attenuated the durations of horizontal movement, rearing, and stereotypy times in a dose × time block interaction manner. By the 10-min block, dosages of 0.05, 0.10, and 1.00 mg/kg SCH23390 clearly inhibited the durations and by time block 20 min the effects were at the maximum. Following the 60-min time block, all behavioral differences were not significant. SCH23390 has been reported to potentiate the duration of various measures of immobility in a dose- and time-dependent manner where the effectiveness was relatively brief (11). These present data, in part, replicate the immobility paradigm study (11), as well as the general description for the locomotor studies (5,6,15).

The D_1 antagonist SK&F83566 also attenuated the durations of horizontal movement, rearing, and stereotypy times in a dose × time block interaction function. However, when comparing comparable dose levels with SCH23390 this antagonist had less attenuating effects across the various measures of locomotor behaviors. These data were similar to those obtained using an immobility model (11).

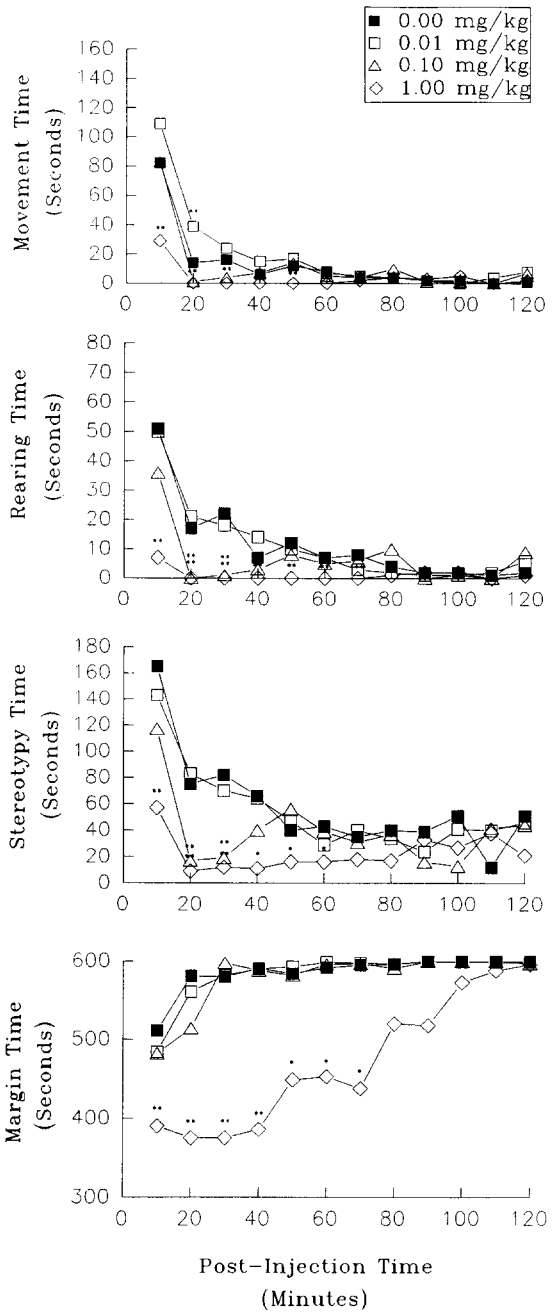

FIG. 2. Effects of several dosages of the dopamine D_1 antagonist SK&F83566 on four measures of locomotor activity (in seconds) over 120 min: Horizontal movement, rearing, stereotypy, and margin times. Significant differences from the vehicle control group (0.00 mg/kg) at each time point: $*p < 0.05$, $**p < 0.01$. For clarity, the error bars have not been included.

Thigmotaxis or wall-seeking behavior, as measured by margin time, was differentially influenced by these two D_1 antagonists. The larger doses of SCH23390 (0.05–0.2 mg/kg) resulted in an earlier thigmotaxis, whereas the largest dose

of SK&F83566 (1.00 mg/kg) attenuated thigmotaxis. While differential change in thigmotaxis has been suggested as an indicator for emotionality in rodents, other paradigms must be used to verify the present observation.

In general, it appears that the D_1 antagonists potentiate the duration of disparate locomotor behaviors, as well as various models of immobility responses. Of particular interest was the fact that these D_1 antagonists have striking similarities to the attenuated behavioral profiles of various D_2 antagonists but not their time courses.

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