Pharmacology Biochemistry and Behavior, Vol. 42, pp. 163–168, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Reinforced Responding of the 11-Day-Old Rat Pup: Synergistic Interaction of D_1 and D_2 Dopamine Receptors

SANDERS A. McDOUGALL,*[1]
CYNTHIA A. CRAWFORD† AND ARTHUR J. NONNEMAN†[2]

**Department of Psychology, California State University, San Bernardino, CA 92407*
†Department of Psychology, University of Kentucky, Lexington, KY 40506-0044

Received 5 July 1991

McDOUGALL, S. A., C. A. CRAWFORD AND A. J. NONNEMAN. *Reinforced responding of the 11-day-old rat pup: Synergistic interaction of dopamine D_1 and D_2 dopamine receptors.* PHARMACOL BIOCHEM BEHAV **42**(1) 163–168, 1992.—Reinforced responding of 11-day-old rat pups was assessed after blockade of D_1 and D_2 dopamine receptors. Initially, rat pups were trained to traverse a straight alley for nipple attachment reward. Rat pups were than injected IP with either the D_1 antagonist SCH 23390 (0.01, 0.015, 0.03, or 0.1 mg/kg), the D_2 antagonist sulpiride (15 or 50 mg/kg), or a combination of SCH 23390 (0.015 mg/kg) and sulpiride (15 mg/kg). The approach performance of drug-treated pups was then compared to vehicle-treated pups on both reinforcement and extinction trials. Sulpiride (15 mg/kg) did not affect either the extinction or reinforced responding of 11-day-old rat pups. In contrast, SCH 23390-treated pups showed significantly longer response latencies than the vehicle controls in both extinction and reinforcement conditions. Combined treatment with SCH 23390 and sulpiride produced the longest response latencies. Analyses of "best score" and frequency data indicated that the drug-induced decline in responding was due to effects on both reward processes and motor capability. The combined results indicate that D_1 and D_2 receptors interact complexly to affect reinforced responding.

Dopamine D_1 D_2 Reward Rat pup SCH 23390 Sulpiride

INTRODUCTION

DOPAMINE (DA) receptor antagonists induce extinction-like responding in rats when either food, water, saccharin, or brain stimulation is used as reward (30,33). Reinforced responding is depressed by antagonists of both the D_1 and D_2 DA receptor subtypes (5,13,22,23,25); however, it is uncertain what role each receptor subtype plays in reinforcement. In a new model of reinforcement, Miller, Wickens, and Beninger (20) propose that D_1 receptors mediate reward directly whereas D_2 receptors affect reward indirectly by mediating the motor performance associated with reward. Thus, according to this model, both D_1 and D_2 antagonists should diminish reinforced responding: the D_1 antagonist by blocking reward and the D_2 antagonist by blocking reward-associated performance. In contrast with this model, other researchers do not ascribe a secondary function to D_2 receptors and suggest that both D_1 and D_2 antagonists directly attenuate reward independent of effects on performance (23,33).

Recently, we have shown that DA receptor systems are involved in the reinforced responding of the preweanling rat pup (19). In these experiments, the responding of 17-day-old rat pups was disrupted by SCH 23390 (a selective D_1 receptor antagonist), yet left unaffected by sulpiride (a selective D_2 receptor antagonist). When given jointly, sulpiride potentiated SCH 23390's response-suppressing effects (19). In total, these results suggest that the role of D_2 receptors in the reinforcement processes of 17-day-old rat pups is not of the same magnitude as in the adult. This is consistent with Miller et al.'s (20) proposal that D_2 antagonists should affect neither reward *or* performance in young rat pups. Their rationale is that cholinergic interneurons in the striatum, which are inhibited by D_2 receptor stimulation, do not become functional in the rat until about 14 days after birth (20). Thus, previous to this age, D_2 antagonist drugs should simply block a still nonfunctional system. In the present study, the reinforced responding of 11-day-old rat pups was assessed after treatment with selective D_1 and D_2 antagonists. If Miller et al.'s (20) model of reward is correct, the reinforced responding of the 11-day-old rat pups should be unaffected by a D_2 antagonist (sulpiride) and diminished by a D_1 antagonist (SCH 23390).

[1] To whom reprint requests should be addressed.
[2] Present address: Department of Psychology, Asbury College, Wilmore, KY 40390.

METHOD

Animals

Subjects were 113 male and female rat pups of Sprague-Dawley descent (Harlan) tested at 11 days of age. Litters were culled to a maximum of 10 pups or a minimum of 8 pups at 3 days of age. Pups were kept with the dam until initial isolation 16 h prior to testing. Assignment of subjects to groups was random according to gender and within each litter. The colony room was maintained at 23–25°C and kept under a 14 L: 10 D cycle. Behavioral testing was conducted during the light phase of the cycle.

Drugs

SCH 23390 (Research Biochemicals Inc., Natick, MA) was dissolved in distilled water; whereas, sulpiride (Sigma, St. Louis, MO) was dissolved in a minimal amount of glacial acetic acid and diluted with distilled water. Both drugs were injected IP at a volume of 5.0 ml/kg, the typical volume for pups of this body weight.

Apparatus

The testing apparatus was a straight alley (40 × 8 × 15 cm) with start and goal boxes (15 × 15 × 15 cm) located at either end. The alley and goal boxes were painted black, and the start box was gray.

Clear Plexiglas basket cages (45 × 21 × 24 cm) containing hardwood chip bedding (Sani-chips) were used as isolation cages and intertrial interval (ITI) chambers. The isolation cages, ITI chambers, and straight alley were located in a separate experimental room. Both the isolation cages and the ITI chambers were placed on heating pads so that pups could be maintained at 33°C, which is approximate thermoneutrality for pups between the ages of 10 and 20 days of age (9).

General Procedure

Approximately 16 h (±1 h) prior to testing, pups were removed from their mother and placed in an isolation cage without available food or water. After the 16-h isolation period, a pup was placed in the goal box of the straight alley and allowed 15-s nipple attachment to an anesthetized dam. Anesthetization was produced by IP injections (2 ml/kg) of L.A. Thesia [chloral hydrate (60 mg/ml) and sodium pentobarbital (30 mg/ml)] starting 20 min prior to testing. In addition to its anesthetic properties, L.A. Thesia blocks milk release, thus producing a reinforcer that has potent rewarding properties yet is not prone to satiation problems (1). After the initial 15-s nipple attachment, the pup was placed in the start box for the beginning of acquisition training. If the pup did not traverse the start box and alley after 60 s, it was gently forced down the alley to the goal box. In either case, 15-s nipple attachment reward was provided and followed by a 15-s placement in the ITI chamber. Acquisition of the approach response consisted of two eight-trial acquisition sessions separated by a 5-min placement in the ITI chamber.

The single testing session began 30 min after the two eight-trial acquisition sessions and included four acquisition trials immediately followed by either 36 reinforcement trials (responding resulted in 15-s confinement with the dam) or 36 extinction trials (responding resulted in 15-s confinement in the empty goal box). During the testing session the rat was not forced down the alley for nonresponding; rather, after 60 s the rat was given a 15-s placement in the ITI chamber.

Experiment 1

A total of 49 11-day-old rat pups were injected with either vehicle, sulpiride (15 or 50 mg/kg), or SCH 23390 (0.01, 0.03 or 0.1 mg/kg) immediately after the second acquisition session and 30 min prior to the testing session. Two vehicle-treated groups were used: one group received reinforcement trials and the other group received extinction trials during the testing session. Therefore, there were a total of seven groups ($n = 7$) with all of the drug groups and one of the vehicle groups receiving reinforcement trials during the testing session.

Experiment 2

A total of 64 11-day-old rat pups were injected with either vehicle, sulpiride (15 mg/kg), SCH 23390 (0.015 mg/kg), or a combination of sulpiride (15 mg/kg) and SCH 23390 (0.015 mg/kg) immediately after the second acquisition session and 30 min prior to the testing session. The four drug conditions were further subdivided, with half of the rat pups ($n = 8$) receiving reinforcement trials during the testing session and the other half receiving extinction trials.

Statistical Analyses

Analyses of variance (ANOVAs) with repeated measures were used to analyze latencies to traverse the maze (combined start box and alley latencies). ANOVAs were performed across blocks of four trials and were supplemented, when appropriate, by Newman-Keuls and Dunnett's tests ($p < 0.05$).

RESULTS

Experiment 1

The mean response latencies of the 11-day-old rat pups declined from the first block (mean = 36.07 s) to the second block (mean = 10.98 s) of the initial acquisition session, $F(1, 42) = 164.82$, $p < 0.0001$ (data not shown). After this initial decline in response latencies, no additional changes were apparent. Additional analyses indicted that groups that subsequently received the different drug treatments and reinforcement conditions responded similarly during the acquisition sessions.

Mean latencies to traverse the maze during the single testing session for the 11-day-old rat pups are presented in Fig. 1. During the ten-block testing session, extinction training was not begun for the vehicle-extinction (VEH-EXT) group until block 2; therefore, the initial block of trials was analyzed separately from the subsequent nine blocks. Across the initial block of four trials, pups receiving the greatest dose of sulpiride (50 mg/kg) had significantly longer response latencies than either of the saline-treated groups or the 15 mg/kg sulpiride group, $F(3, 24) = 6.36$, $p < 0.01$. Likewise, the response latencies of rat pups injected with the two largest doses of SCH 23390 (0.03 and 0.1 mg/kg) were significantly longer than the latencies of the saline- or 0.01 mg/kg SCH 23390-treated pups, $F(4, 30) = 3.51$, $p < 0.05$. During the initial block of trials, the 11-day-old pups receiving 15 mg/kg sulpiride or 0.01 mg/kg SCH 23390 did not differ from the vehicle-treated pups.

Across the remaining nine blocks of trials, vehicle-treated pups given extinction trials had significantly longer response latencies than did the vehicle-treated pups continued on reinforcement, $F(1, 12) = 4.42$, $p < 0.05$. Sulpiride treatment differentially affected responding according to dose, as the 11-day-old pups given the greater dose of sulpiride (50 mg/

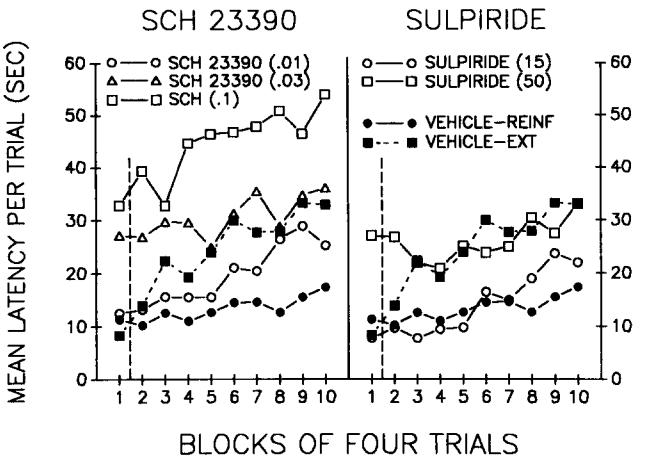

FIG. 1. Mean response latencies across blocks of four trials for 11-day-old rat pups injected with either vehicle, SCH (0.01, 0.03, or 0.1 mg/kg, IP) or sulpiride (15 or 50 mg/kg, IP), 30 min prior to the testing session. All of the drug groups and one of the vehicle groups received reinforcement (REINF) trials during the testing session, whereas the other vehicle group received extinction (EXT) trials.

kg) responded like the VEH-EXT group; whereas the pups given 15 mg/kg sulpiride responded like the vehicle-reinforcement (VEH-REINF) groups, $F(3, 24) = 3.12, p < 0.05$. SCH 23390 also affected responding, as the pups receiving the two greatest doses of SCH 23390 (0.03 and 0.1 mg/kg) had significantly longer response latencies than the VEH-REINF group, $F(4, 30) = 7.79, p < 0.001$. Pups injected with the intermediate dose of SCH 23390 (0.03 mg/kg) responded no differently than the VEH-EXT group; whereas pups in the 0.1 mg/kg SCH 23390 group had longer response latencies than pups given extinction trials. The mean response latencies of pups in the 0.01 mg/kg SCH 23390 group were intermediate between the VEH-EXT and VEH-REINF groups and did not differ significantly from either. All of the comparisons mentioned are collapsed across the testing session, because the interactions involving Block as a variable were not significant.

To help assess whether the drugs were affecting reward processes or motor capability, the patterns of individual latency scores for the pups receiving vehicle were compared with latencies of pups receiving drug injections (31,32). If the drug was exclusively affecting motor capability independent of any action on reward processes, it would be predicted that the pattern of latency score frequency would be similar among the drug and VEH-REINF groups, but that the drug would cause a uniform shift in latency scores across the whole distribution. In contrast, if the drug was exclusively affecting reward processes it would be expected that the latency score frequency distribution of the drug group would be similar to the distribution of the VEH-EXT group. In addition, if the drug produced a state similar to extinction it would be expected that both drug and vehicle groups should have at least some trials in which the latencies were very short ("best scores"), especially at the start of the testing session.

Frequency distributions of latencies to traverse the alley are presented in Fig. 2. The frequency distributions for pups receiving high doses of SCH 23390 (0.03 and 0.1 mg/kg) and sulpiride (50 mg/kg) suggested some motor impairment, as the latency score frequencies of these drug-treated groups did not reflect the latency scores of the VEH-EXT groups. For example, pups in the VEH-EXT group had twice as many latency scores fall between 1.2 and 2.2 s as did pups receiving 0.03 mg/kg SCH 23390 (pups receiving 0.1 mg/kg SCH 23390 and 50 mg/kg sulpiride had almost no scores in this range). Modal scores of the 0.03 mg/kg SCH 23390 group and the VEH-EXT group also differed, with the mode of the SCH 23390 group (3.6 s, 19 scores) shifted to the right of the VEH-EXT group (2.2 s, 21 scores). The frequency distribution for the VEH-REINF group is not presented, since the drug groups responded more like the VEH-EXT group (see Fig. 3 for a representative frequency distribution from a VEH-REINF group). A best scores analysis also indicates some motor impairment: as the best scores for pups in the VEH-EXT group (1.2 s, four scores) were shorter than the best scores for the 0.1 mg/kg SCH 23390 group (2.0 s, two scores) and the 50 mg/kg sulpiride group (1.9 s, two scores). Thus, these results indicate that the greater doses of sulpiride (50 mg/kg) and SCH 23390 (0.03 and 0.1 mg/kg) did not affect reward processes exclusive of actions on motor performance; whereas the lesser doses of sulpiride (15 mg/kg) and SCH 23390 (0.01 mg/kg) did not significantly affect the reinforced responding of 11-day-old rat pups.

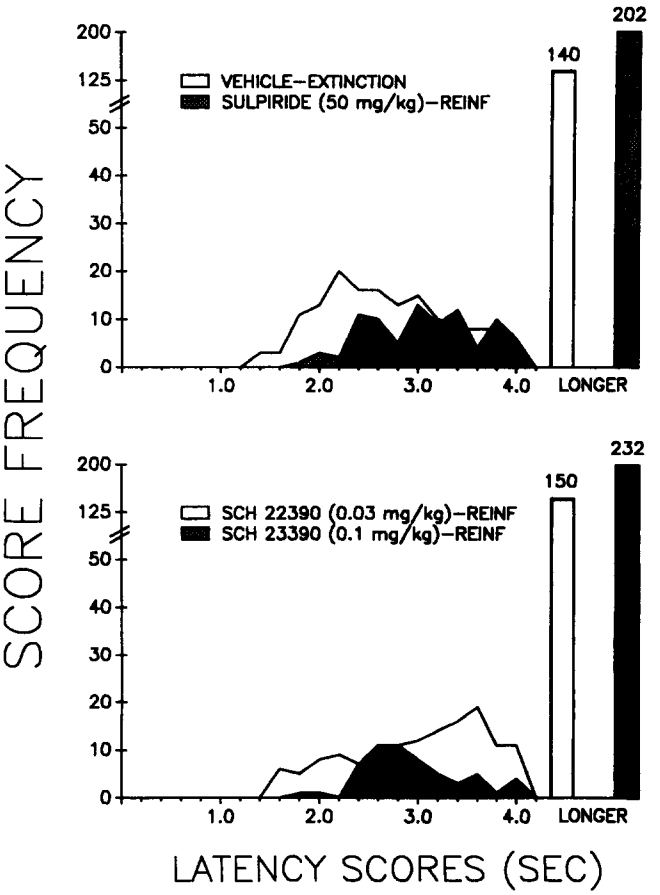

FIG. 2. Frequency distributions of alley-way latency scores during the testing session. The groups represented were injected with either vehicle, sulpiride (50 mg/kg), or SCH 23390 (0.03 or 0.1 mg/kg) 30 min prior to the testing session. During the testing session drug-treated pups were given reinforcement (REINF) trials, whereas the vehicle group was given extinction trials.

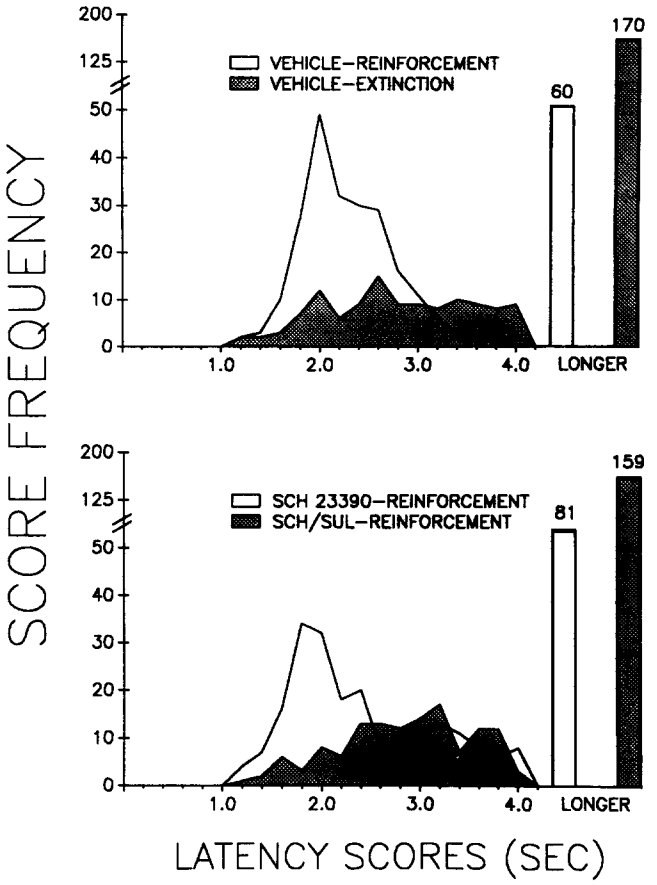

FIG. 3. Frequency distributions of alley-way latency scores during the testing session. The groups represented received injections of either vehicle, SCH 23390 (0.015 mg/kg), or a combination of SCH 23390 (0.015 mg/kg) and sulpiride (15 mg/kg) 30 min prior to testing. During the testing session drug-treated pups were given reinforcement trials, whereas the two vehicle groups were given either reinforcement or extinction trials.

Experiment 2

The pattern of results during sessions 1 and 2 of Experiment 2 are substantially the same as those of the previous experiment, as rat pups had progressively shorter response latencies across the two blocks of the initial acquisition session, $F(1, 56) = 119.74, p < 0.0001$. After this initial decline in response latencies, no additional changes were observed.

Mean latencies to traverse the maze during the single testing session for the 11-day-old rat pups are presented in Fig. 4. During the initial block of trials, pups receiving the combined SCH 23390 and sulpiride (SCH/SUL) treatment had significantly longer response latencies than pups in the other drug and vehicle groups, $F(3, 56) = 6.68, p < 0.001$.

During the remaining nine blocks of trials, vehicle-treated pups given extinction trials had significantly longer response latencies than pups in the VEH-REINF group, $F(1, 14) = 70.28, p < 0.0001$. This effect varied according to block, as the VEH-REINF group maintained a stable level of responding across the testing session; whereas the VEH-EXT group had longer response latencies as the testing session progressed, $F(8, 112) = 10.33, p < 0.0001$. This pattern of responding was also observed in the various drug groups, as the sulpiride-, SCH 23390-, and SCH/SUL-treated pups tested under reinforcement conditions did not show a block-dependent change in responding. In contrast, when given extinction trials, all drug groups showed a significant increase in response latencies as the testing session progressed, $F(8, 224) = 35.69, p < 0.0001$.

Responding of the 11-day-old rat pups was affected by drug treatment under both extinction and reinforcement conditions. During extinction testing, pups given combined SCH/SUL treatment had significantly longer response latencies than vehicle-treated pups, $F(3, 28) = 4.12, p < 0.05$. The other drug groups did not differ from the vehicle group during extinction testing. When tested under reinforcement conditions, the SCH/SUL group also had longer latency scores than the vehicle group, but in this condition the latencies of the SCH 23390-treated pups were intermediate between, and significantly different from, the vehicle and SCH/SUL groups, $F(3, 28) = 12.19, p < 0.0001$. The sulpiride- and vehicle-treated pups did not differ.

To help determine whether the SCH 23390 and SCH/SUL treatments were primarily affecting reward processes or motor ability, the patterns of individual latency scores were compared. Frequency distributions of latencies to traverse the alley for both the SCH-REINF and SCH/SUL-REINF groups, relative to vehicle controls, are presented in Fig. 3. The frequency distributions of the SCH/SUL-REINF group and the VEH-EXT group are similar and suggest that this combination of drugs was affecting reward processes. A best scores analysis is also consistent with a reward interpretation, as the best scores for all groups in the experiment were similar. In contrast, the dissimilarity between the SCH-REINF and VEH-EXT curves is not consistent with a reward interpretation.

DISCUSSION

Although it is now apparent that DA receptor systems mediate reinforcement processes, it is uncertain how D_1 and D_2 receptors interact to affect these processes. In the present

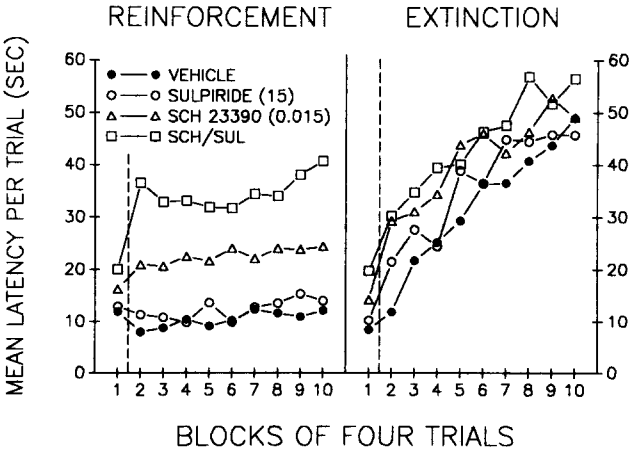

FIG. 4. Mean response latencies across blocks of four trials for 11-day-old rat pups injected with either vehicle, sulpiride (15 mg/kg), SCH 23390 (0.015 mg/kg), or a combination of sulpiride (15 mg/kg) and SCH 23390 (0.015 mg/kg) 30 min prior to the testing session. All groups were tested under both reinforcement and extinction conditions.

study, a 15 mg/kg dose of sulpiride did not affect the reinforced responding of 11-day-old rat pups. The lack of a sulpiride-induced effect was not due to a lack of drug efficacy, as similar doses of sulpiride completely antagonize the quinpirole-induced locomotor activity of 11-day-old pups (18). A greater dose of sulpiride (50 mg/kg) did diminish the reinforced responding of the pups; however, this was apparently due to a decline in motor ability and not due to changes in reward value. For example, pups injected with 50 mg/kg sulpiride did not show a typical extinction-like curve, but rather showed an immediate and substantial increase in response latencies. Furthermore, best score data indicated that pups given 50 mg/kg sulpiride could not approach the dam as quickly as vehicle-treated pups.

The D_1 receptor antagonist also affected the reinforced responding of 11-day-old rat pups. In Experiment 1, a 0.01 mg/kg dose of SCH 23390 was insufficient to affect responding; whereas, greater doses of SCH 23390 exhibited a drug-induced decrement in performance on the first block of the testing session. In Experiment 2, an intermediate dose of SCH 23390 (0.015 mg/kg) was used in an attempt to show a drug-induced decrease in responding independent of effects on motor ability. This dose of SCH 23390 (0.015 mg/kg) did increase the response latencies of the rat pups during reinforcement but not extinction testing. However, two characteristics of the data make it doubtful whether the SCH 23390 was affecting reward processes exclusively: First, as can be seen in Fig. 4, the SCH 23390–treated pups maintained a stable level of responding across the testing session, quite unlike the VEH-EXT or SCH-EXT groups. Second, as can be seen in Fig. 3, the frequency distribution of the SCH-REINF group was much more similar to the VEH-REINF group than to the VEH-EXT group. Thus, it appears that SCH 23390 affected both reward and nonreward processes.

Combined treatment with both D_1 and D_2 antagonists produced the most profound disruption of responding, as the SCH 23390–induced increase in response latencies was further potentiated by sulpiride (15.0 mg/kg). This potentiation effect was observed only when responding was reinforced and not during extinction testing. Analysis of the frequency distributions and best scores of the SCH/SUL and VEH-EXT groups was consistent with a reward interpretation (see Fig. 3); however, the dissimilar response patterns of the SCH/SUL-REINF and the SCH/SUL-EXT and VEH-EXT groups suggests that the drugs were not affecting reward independent of motor performance (see Fig. 4). For example, the SCH/SUL-EXT and VEH-EXT groups showed a block-dependent increase in response latencies; whereas the SCH/SUL-REINF groups maintained a stable level of responding across the testing session. Moreover, during the first half of the testing session, the response latencies of the SCH/SUL-REINF group were longer than those of the VEH-EXT group. Therefore, these results indicate the SCH and SCH/SUL treatments did not exclusively affect reward processes; however, these results also indicate that reinforced responding of 11-day-old pups is mediated, at least partially, by a complex interaction of D_1 and D_2 receptors.

The ability of sulpiride to potentiate the SCH 23390–induced disruption of reinforced responding is interesting and provides further evidence that D_1 and D_2 receptors are coupled in some fashion. The DA literature is replete with behavioral evidence for a functional interaction between D_1 and D_2 receptors (2,8,28), but this evidence has usually taken one of two forms. First, in both young and adult rats the D_1 receptor system appears to play a "permissive" role for D_2 agonist–induced behaviors, as D_1 antagonists block the enhanced sniffing, yawning, and locomotor activity induced by D_2 agonists (15,18,24,26). Although less certain, it also appears that a functioning D_2 system is necessary for the occurrence of D_1-mediated grooming behavior (14,21). Second, some behaviors (e.g., licking/biting, climbing, gnawing, and stereotyped behaviors) are fully exhibited only after treatment with a combination of selective D_1 (e.g., SKF 38393 and SKF 82526) and D_2 (e.g., quinpirole, RU 24213, and bromocriptine) agonists or a mixed D_1/D_2 agonist (e.g., apomorphine) (4,6,10,16,17). These behaviors are then eliminated or substantially reduced by either a D_1 or D_2 antagonist (4,6,10,16). More rare are studies showing that joint antagonism of both D_1 and D_2 receptors produces additive effects on behavior (3,18,29). For example, Wanibuchi and Usuda (29) have shown that maximal catalepsy is produced by combined treatment with SCH 23390 and YM-09151 (a D_2 antagonist); whereas Arnt and Hyttel (3) have shown that the apomorphine-induced circling of 6-hydroxydopamine-lesioned rats was completely blocked by combined treatment with SCH 23390 and spiroperidol (a D_2 antagonist). In the present study, reinforced responding of 11-day-old rat pups was maximally disrupted by joint treatment with SCH 23390 and sulpiride. These results show that an adult-like interaction between DA receptor subtypes is apparent in rats as young as 11 days of age.

In their model of reinforcement, Miller et al. (20) suggest that both D_1 and D_2 receptors are involved in reinforcement processes: D_1 receptors primarily mediate reward, while striatal D_2 receptors mediate reward-associated performance. In rat pups, however, Miller et al. (20) predict that only D_1, and not D_2, antagonists should disrupt reinforced responding. Their reasoning is that the cholinergic component of the striatal matrix presumed to mediate performance is not functionally mature prior to 14 days of age (20). These predictions were only partially supported by the present results. For example, SCH 23390 may have reduced the reward value of the dam, but this could not be separated from effects on motor performance. As predicted, blockade of D_2 receptors by an efficacious dose of sulpiride (15 mg/kg) did not affect the reinforced responding of 11-day-old rats. However, when combined with SCH 23390, sulpiride maximally disrupted responding, indicating that D_2 receptors may play an important role in the reinforced responding of 11-day-old rat pups.

It has previously been reported that DA antagonists produce fewer cataleptogenic effects in younger rat pups than older pups or adults (7,12). If correct, the 11-day-old pup would seem to provide an excellent model for studying reinforcement processes, since the potential of drug-induced motor incapacitation has complicated data interpretation in reward studies using the adult (11,27). Unfortunately, the 11-day-old rats' motor performance appears to be disrupted by even small doses of SCH 23390 (0.03 mg/kg) and moderate doses of sulpiride (50 mg/kg). These same doses did not produce motor disturbances in 17-day-old rat pups when tested on the identical task (19). The discrepancy between these results and those of previous studies, which showed that younger pups are less affected by DA antagonists, is probably task dependent. For example, Fitzgerald and Hannigan (12) found that greater doses of SCH 23390 were required to induce catalepsy in younger rat pups. In contrast, we assessed performance on an appetitive approach task, a behavior that is both goal-directed and requires planned motor movements. Therefore, it appears that younger rat pups have an enhanced sensitivity to DA antagonists when behavior is assessed on instrumental tasks rather than with unlearned behaviors.

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