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D_2-Specific Discriminative Stimuli: Parameters, Blocking, and Rebound

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HUFFMAN, E. M., W. F. CAUL, E. J. STRAND, J. R. JONES AND R. J. BARRETT. *D_2-specific discriminative stimuli: Parameters, blocking, and rebound.* PHARMACOL BIOCHEM BEHAV **51**(1) 77-82, 1995.—This study characterizes the cue properties of quinpirole (LY 171555), a selective D_2 agonist, and the blocking capabilities of spiperone, a selective D_2 antagonist. After rats were trained to discriminate 0.025 mg/kg quinpirole from distilled water, a dose-response curve and time course of the quinpirole discriminative stimulus were determined. The effectiveness of three doses of spiperone in blocking the discriminative stimulus produced by 0.02 mg/kg quinpirole was then assessed. Finally, the time course of spiperone's blocking action was determined. Given the putative selective action of these drugs on D_2 receptors and the parametric data presented here, it was predicted that following chronic treatment with spiperone, a rebound increase in quinpirole-appropriate responding would occur. Neither chronic treatment with spiperone nor chronic treatment with haloperidol produced the predicted changes. This result, however, may be confined to the specific dose and time parameters used.

D_2-discriminative stimuli Rebound changes in discriminative states Chronic treatment
Quinpirole Spiperone

UNDERSTANDING the effects of dopamine agonists and antagonists is important given the involvement of dopaminergic systems in a wide range of behaviors (21), reward system function (25), neurologic disorders (15), and psychopathology (19). The identification of multiple dopamine receptor subtypes that comprise D_1 and D_2 families (16) has added the need to understand the functional roles and interactions of these receptor subtypes in behavior.

Research using the drug-discrimination procedure has been useful in characterizing stimulus properties of dopamine agonists, as well as in assessing the ability of dopamine antagonists to block agonist-induced discriminative stimuli. This research includes identifying stimulus properties of drugs that act at selective dopamine receptor subtypes (13,24,26), and investigating the potential interactions between D_1 and D_2 dopamine receptors (5,12,14,23).

In discrimination learning, it is important to present precisely defined discriminative stimuli repeatedly during the course of training. It is imperative to carefully use the same dose of drug and the same interval between injection and training sessions, because any drug effects remaining from one drug administration to the next will alter the drug-produced interoceptive stimulus. Thus, it becomes important to determine the time course of drug-produced stimuli so that appropriate interdose intervals can be used and the possibility of cumulative drug effects can be eliminated. This concern applies to all drug-discrimination work, but it is especially relevant to the use of drug-drug discriminations that involve an agonist and an antagonist that act on the same neurotransmitter system (17). Drug-discrimination research of this nature suggests that animals trained to discriminate an agonist from an antagonist respond on the basis of a continuum of neurotransmitter function (1), and that such responding can illustrate rebound changes in discriminative stimuli (3,8,10).

Drug discrimination studies using the indirect dopamine agonist amphetamine have investigated rebound shifts along this continuum resulting from administration of the mixed D_1/D_2 antagonist haloperidol. In animals trained to discriminate between amphetamine and saline, administration of haloperidol produces increased amphetamine-appropriate lever responding when animals are tested without drug. This shift in baseline responding has been demonstrated following chronic

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haloperidol treatment (2), as well as 23 h after a single dose of haloperidol (6).

Similarly, when animals are trained to discriminate amphetamine from haloperidol in a drug-drug discrimination, chronic treatment with the training drugs produces rebound changes in discriminative stimuli. Following acquisition of the discrimination, rebound changes in discriminative stimuli were shown as increased amphetamine-appropriate lever responding following chronic haloperidol treatment and increased haloperidol-appropriate lever responding following chronic amphetamine treatment (3,10). Similar rebound changes are produced following a single dose of amphetamine or haloperidol (3). The drug-drug discrimination procedure used in this research provides a sensitive measure of discriminative stimulus change over time and is useful for identifying relationships between sensitization, tolerance, and withdrawal.

The above series of studies used drugs with mixed dopamine receptor activity. The present research is concerned with the properties of two D_2-specific drugs; the agonist quinpirole and the antagonist spiperone. Although these two drugs have specific dopamine D_2-receptor subtype activity (20), recent reports indicate that quinpirole has potent D_3 activity as well (9,13). Although three previous studies have used quinpirole successfully in a drug-saline discrimination (9,22,23), temporal parameters of the drug-produced cue have not been reported, and the ability of spiperone to block the quinpirole-produced cue has not been assessed. Similarly, although spiperone has been used for some time to block cues thought to be mediated by D_2 receptors (4,7,12), temporal parameters of this blocking effect have not been published. Experiment 1 of the present research addresses these issues.

With the information regarding the dose and temporal parameters of quinpirole and spiperone provided by Experiment 1, these drugs can be used in evaluating a range of questions concerning phenomena such as sensitization, tolerance, and withdrawal. Consistent with the logic developed in this line of research (3), if spiperone blocks the quinpirole-produced discriminative stimulus and hence acts on the same neurotransmitter system or systems, then quinpirole choice responding—i.e., spiperone rebound responding—should be observed at certain time intervals following chronic spiperone administration. Experiment 2 addresses this prediction.

EXPERIMENT 1

Purpose

The purpose of the first experiment was to characterize the discriminative stimulus properties of quinpirole (LY 171555) and the ability of the selective D_2 antagonist spiperone (11) to block the quinpirole-produced cue. Effective dose and time parameters were examined.

Method

Animals. Thirty male Sprague-Dawley rats (Harlan Co., Indianapolis, IN), 73 days of age, were maintained on a 12 L : 12 D cycle (0700–1900 h light).

Apparatus. Six operant boxes were used. The front panel of each box was divided into thirds by two clear plastic dividers that extended from the ceiling to the grid floor and protruded 6.0 cm into the chambers. Each of the three divisions could be equipped with a response lever. The pellet hopper was mounted on the opposite back panel. Each operant box was located within a sound-attenuating chamber that was supplied with white noise. The house light in each box was illuminated at the beginning of each session and extinguished when the session ended. Experimental sessions were controlled by a version of the software package described in previous research (18).

Chemicals. The drugs used were quinpirole hydrochloride and spiperone hydrochloride (Research Biochemicals Inc., Natick, MA). Both drugs were dissolved in deionized water and administered in volumes of 1 ml/kg.

Procedure

Preliminary training. At approximately 80 days of age, the animals were placed on a food deprivation schedule to reduce their weight by 15%. This schedule involved providing appropriate amounts of powdered food to attain target weights. Once achieved, these target weights were maintained throughout the experiment by supplementing the food pellets earned during experimental sessions with powdered food in the home cage immediately following the experimental sessions.

Ten days after the onset of the food deprivation schedule, 20-min training sessions were begun with only the center lever present. Animals were trained to press the lever using food reinforcement (45 mg; P.J. Noyes Co.) for each response. Training was continued until a criterion of 100 responses per 20-min session was met. After this criterion was met during subsequent sessions with only the right or the left lever present, an additional session with each of the levers was conducted using a variable-interval 10-s schedule of reinforcement (VI-10).

Discrimination training. Acquisition sessions were conducted with both the left and right levers present. Each session lasted 20 min. Twenty minutes before each training session, the animals were injected subcutaneously with either 0.025 mg/kg quinpirole or distilled water. On each training day, five squads of six animals each were run in random order. The drug-appropriate levers were counterbalanced within squads. These precautions were taken to ensure that odor cues were nonpredictive of the correct lever. Acquisition sessions were conducted every other day. Drug-appropriate lever responding was reinforced under the VI-10 schedule. A single-alternation schedule of distilled water and quinpirole was used.

To assess acquisition of discrimination unconfounded by the presence of reinforcement, acquisition sessions on training days 5, 6, 11, 12, 17, 18, 23, 24, 29, 30, 35, and 36 started with a 2.5-min period during which no food pellets were delivered. The remaining 17.5 min of each of these sessions were conducted under the VI-10 reinforcement schedule for correct responding.

After the final acquisition session, animals were matched on the basis of their discrimination performance. Discrimination performance was determined by averaging percent correct lever responding during the initial 2.5 min of session 35 when given distilled water, and percent correct lever responding during the initial 2.5 min of session 36 when given quinpirole. The mean of the discrimination performance for these 2 days provided the basis for rank ordering the subjects. Six animals were discontinued from the experiment at this point either because they failed to meet a criterion of five total responses during the initial 2.5 min of either session, or their mean discrimination performance was among the lowest of the group. The remaining 24 animals were randomly assigned to four groups.

Quinpirole dose-response. Animals in each of the four

groups received either 0.025, 0.0125, 0.00625, or 0.0 mg/kg quinpirole 20 min before testing. No reinforcement was given during the 2.5-min testing session. The dose-response function was assessed a second time, 23 days later.

Quinpirole time course. Following determination of the quinpirole dose-response function, all animals were given a distilled water acquisition session, (i.e., 20 min, VI-10), and a quinpirole acquisition session. The four groups were then used to evaluate the time course of the quinpirole cue. Each group received 0.025 mg/kg quinpirole either 20 min, 1 h, 3 h, or 24 h before the 2.5-min nonreinforced test session.

Spiperone blocking of quinpirole cue. Prior to assessing spiperone's effects, animals were given one acquisition session with distilled water and one session with the training dose of quinpirole. To ensure sensitivity to the blocking effects of small doses of spiperone, the dose of quinpirole administered was 0.020 mg/kg, which was determined from the second dose-response function to be effective in producing approximately 75% quinpirole-lever responding. Forty minutes before the test session, each of the four groups was injected with a different dose of spiperone: 0.02, 0.01, 0.005, and 0.0 mg/kg (DW). Twenty minutes before testing every animal received 0.020 mg/kg quinpirole.

Time course of spiperone blocking effect. The final test, which was also preceded by a distilled water and a quinpirole training session, determined the blocking activity of spiperone as a function of time between the spiperone and quinpirole injections. Each of the four groups received spiperone (0.02 mg/kg) either 20 min, 1 h, 3 h, or 24 hours, before 0.020 mg/kg quinpirole. Animals were given the 2.5-min test session without reinforcement 20 min after the quinpirole injection.

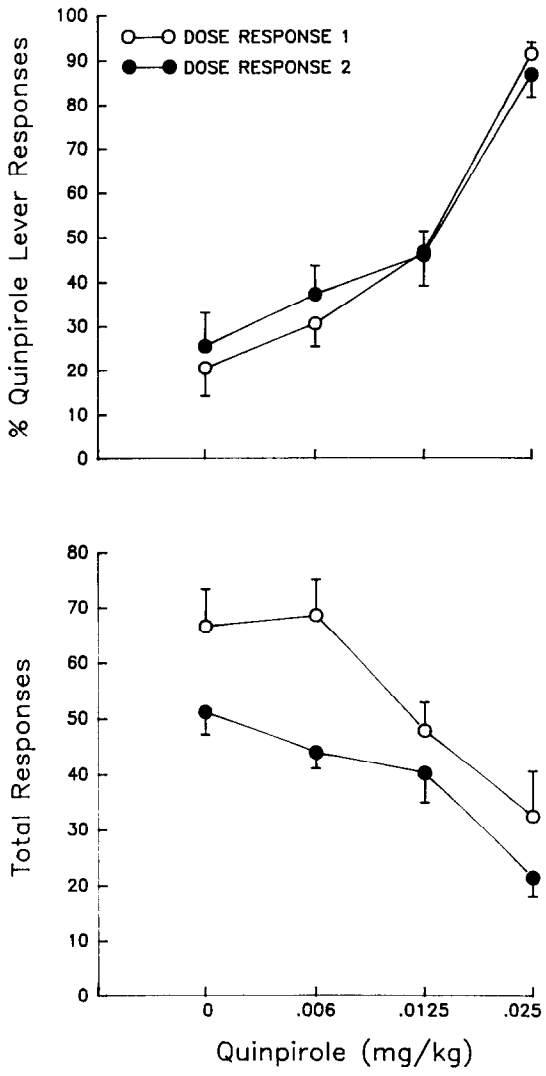

FIG. 1. Percent quinpirole lever responding and total responses as a function of quinpirole dose. Results from two identical tests separated by 23 days are shown.

Results and Discussion

Acquisition. On the final acquisition session with distilled water, (i.e., day 35), the mean number of total responses made during the 2.5-min nonreinforced period was 66.1 (±3.94 SEM). The mean percent correct lever responding was 81.5 (±2.34 SEM). On the final acquisition session with quinpirole, (i.e, session 36), the mean number of responses made during the initial period was 29.0 (±2.51 SEM), and the mean percent correct was 84.7 (±2.30 SEM).

Quinpirole dose-response. The top panel of Fig. 1 shows the dose-response functions for the two independent assessments. Analysis of the data shows that the animals' choice behavior was significantly affected by the dose of quinpirole administered [$F(3, 24) = 42.81, p < 0.001$], and that choice behavior did not differ across the assessments [$F(3, 24) < 1$]. The mean number of responses made during the 2.5-min nonreinforced test session is seen on the bottom panel of Fig. 1. As expected from the response rates during acquisition, the total number of responses depended on the dose of quinpirole administered [$F(3, 24) = 12.98, p < 0.001$], with the number of responses decreasing with higher doses of quinpirole. Although the animals' choice responding to different doses of quinpirole did not change from the first assessment to the second, their mean total number of responses did [$F(1, 24) = 14.31, p < 0.001$]. The mean total number responses for the first dose-response test session was 53.9, whereas it was only 39.2 for the second.

These dose-response data agree with results previously reported (22,24). Percent quinpirole lever responding increased as the dose of the drug was increased. The inverse relationship between quinpirole dose and response rate observed here is also consistent with earlier reports (22,24).

Quinpirole time course. Figure 2 shows the mean percent quinpirole lever responding and the mean total responses made by the four groups of animals that received 0.025 mg/kg quinpirole at intervals of 20 min, 1 h, 3 h, and 24 h before testing. The saliency of the quinpirole cue was highly dependent on the injection-test interval [$F(3, 24) = 21.06, p < 0.001$]. Although the cue remained strong after 1 h, by 3 h after injection only 33.4% of the animals' responses were on the quinpirole lever and, by 24 h, the quinpirole cue was apparently gone. Injection-test interval also had a significant effect on the total number of responses made during the test session [$F(3, 24) = 3.70, p < 0.05$]. Response rates were lowest when the animals responded predominantly on the quinpirole lever, and highest when they responded predominantly on the distilled water lever. In total, these results suggest that an interval of 24 h is appropriate between this dose of quinpirole and the administration of other drugs or vehicle.

Spiperone blocking of quinpirole cue. Figure 3 presents the data for the four groups pretreated with spiperone. Each

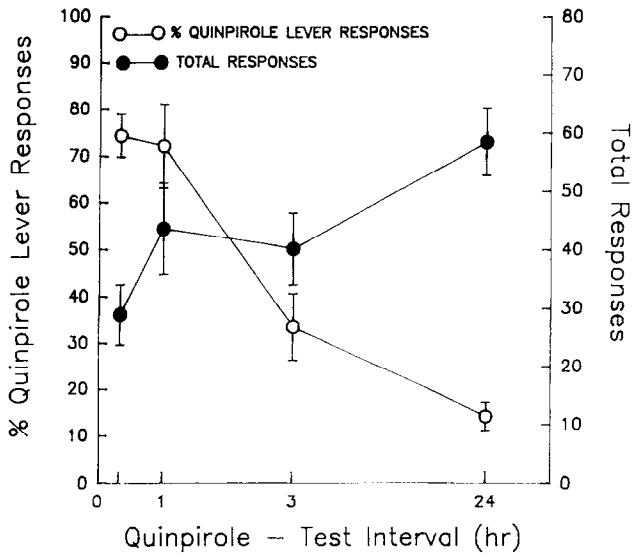

FIG. 2. Percent quinpirole lever responding and total responses as a function of interval between injection and testing. Four groups of animals were tested 20 min, 1 h, 3 h, and 24 h after treatment with 0.025 mg/kg quinpirole.

group was injected with distilled water or spiperone 20 min prior to an injection of 0.020 mg/kg quinpirole. As the figure shows, the saliency of the quinpirole cue was significantly affected by the blocking dose of spiperone [$F(3, 24) = 6.02$, $p < 0.005$]. Specifically, percent quinpirole lever responding steadily decreased as the dose of spiperone increased, reaching a low of 32.0% when 0.02 mg/kg spiperone was administered. Although response rates appear to increase, at least for the two lower doses of spiperone, the change was not large enough for spiperone dose to have a significant effect on the mean total number of responses [$F(3, 24) = 1.60, p = 0.215$].

These data provide evidence that quinpirole's cue properties are mediated, at least in part, by activity at the D_2 receptor, but do not preclude the involvement of other dopamine receptor subtypes. For example, Gui-Hua and Woolverton (9) reported the possible role of D_3 receptor subtype involvement.

Time course of spiperone blocking effect. Figure 4 shows the percent quinpirole lever responding and response rate as a function of time between spiperone injection (0.02 mg/kg) and administration of quinpirole (0.02 mg/kg). The significant effect of injection interval [$F(3, 24) = 11.89, p < 0.001$] and inspection of Fig. 4 suggest that the blocking effect of spiperone diminished little by 3 h and had dissipated completely by 24 h. Although Fig. 4 suggests the mean total responses decreased as quinpirole-appropriate responding increased, the effect of interval between injections was not statistically significant [$F(3, 24) = 1.36$, $p = 0.28$]. These data indicate that the blocking capability of spiperone lasted for at least 3 h and was gone by 24 h.

EXPERIMENT 2

Purpose

Given the parameters outlined earlier and the evidence that spiperone blocks the quinpirole-produced discriminative stimulus, the purpose of the second experiment was to assess the extent to which chronic administration of spiperone might enhance quinpirole-appropriate lever responding.

Method

Animals and apparatus. The thirty male Sprague-Dawley rats that served as subjects in Experiment 1 again served as subjects in Experiment 2. They were maintained on the deprivation schedule described in Experiment 1. The animals were housed and tested in the apparatus previously described.

Chemicals. In addition to quinpirole and spiperone, haloperidol was also used. All drugs were dissolved in deionized water and administered in volumes of 1 ml/kg.

Procedure

Training. Thirty days following the final test session of Experiment 1, the animals were given the first of 16 additional training sessions to discriminate 0.020 mg/kg quinpirole from distilled water. The protocol described in the first experiment was followed. Over the 15th and 16th discrimination sessions, the discrimination performance as determined by mean percent correct lever responding for all 30 animals was 80.74 (±2.30 SEM).

Chronic treatment. Following discrimination retraining, animals were rank ordered based on discrimination performance in the manner described in Experiment 1. Three animals that failed to recover baseline discrimination were discontinued from the study. The remaining 27 animals were randomly assigned to three chronic treatment groups ($n = 9$). The discrimination performance for each group was 80.86 (±4.65 SEM), 82.86 (±3.87 SEM), and 80.96 (±4.13 SEM). The chronic treatment groups received daily SC injections of either 1.0 mg/kg spiperone, 1.0 mg/kg haloperidol, or distilled water for 10 consecutive days. No testing or retraining was conducted during this chronic treatment period.

Rebound testing. Twenty-four hours after the conclusion of the chronic treatment regimen, the animals were tested for rebound changes in discriminative stimuli. Based on the dose-response data illustrated in Fig. 1, 0.00625 mg/kg was determined to be an intermediate dose of quinpirole and was chosen as the test dose. All animals were administered 0.00625

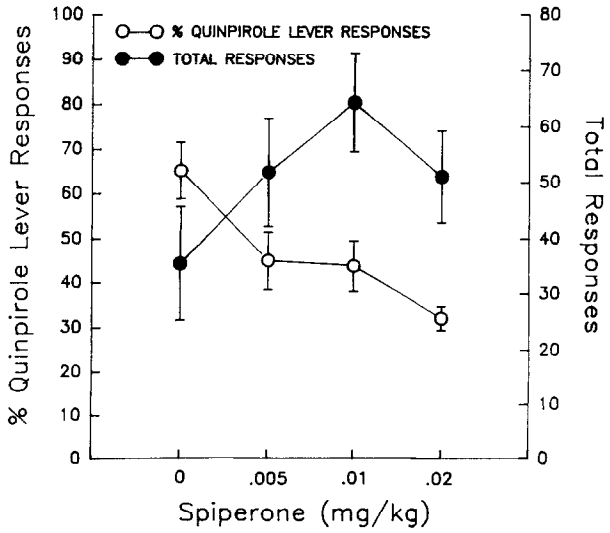

FIG. 3. Percent quinpirole lever responding and total responses as a function of spiperone dose. Four groups of animals were injected with either distilled water, 0.005 mg/kg, 0.010 mg/kg, or 0.020 mg/kg spiperone 20 min before administration of 0.020 mg/kg quinpirole.

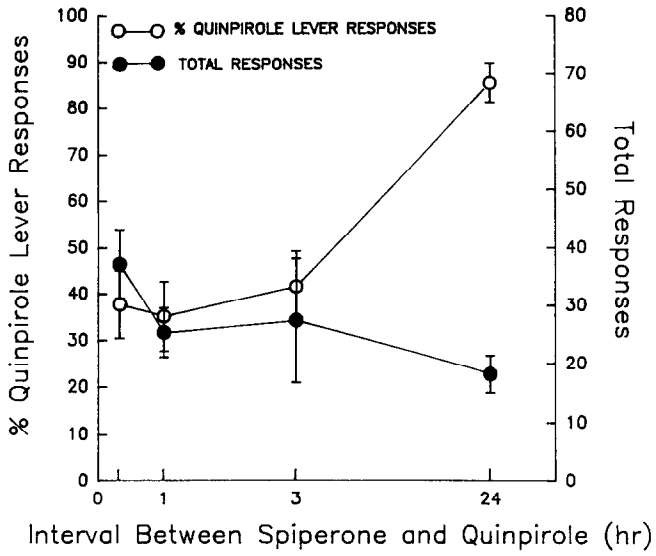

FIG. 4. Percent quinpirole lever responding and total responses as a function of interval between injection of 0.020 mg/kg spiperone and administration of 0.020 mg/kg quinpirole.

mg/kg quinpirole 20 min before testing. The test session consisted of one 2.5-min nonreinforced trial.

Results and Discussion

As before, animals that failed to meet a criterion of five responses during the test session were excluded from this data set. Mean percent quinpirole lever responding for the haloperidol group (n = 8) was 36.25 (±4.45 SEM), for the spiperone group (n = 8) was 34.78 (±3.04 SEM), and for the distilled water group (n = 5) was 63.32 (±7.80 SEM). The results indicate that neither spiperone nor haloperidol effectively enhanced quinpirole choice responding [$F(2, 18) = 9.37$, $p > 0.05$]. There was no significant difference among the spiperone, haloperidol, and distilled water treated animals. Given the strong support for rebound changes in cue state following chronic drug treatment, these results were unexpected. It was concluded that a more sensitive measure may be obtained with minor methodologic revisions. A more stringent discrimination performance criterion for inclusion in the experiment may increase sensitivity. Although the mean percent drug appropriate lever responding during the final two training sessions was 80, the range was 58–100. Testing with animals that discriminate poorly or respond inconsistently may have had adverse affects on the results. Finally, no pretreatment test was given to assess responding before chronic treatment. Inclusion of such a test allows for within-subject comparisons and assessment of prechronic treatment behavior under the testing conditions.

EXPERIMENT 3

Purpose

Experiment 3 included these procedural revisions and reassessed potential rebound changes in discriminative stimuli resulting from chronic drug treatment.

Method

Animals. The thirty male Sprague–Dawley rats described in the previous experiments comprised the subject pool for Experiment 3. The animals were maintained on the same schedule and housed and tested in the previously described apparatus.

Procedure

Training. Starting 14 days following the test session described in Experiment 2, the animals were given 16 additional discrimination training sessions, eight with 0.02 mg/kg quinpirole and eight with distilled water. At the conclusion of the 16th training session, six animals were discontinued from the study because they failed to meet the criterion of responding at least five times during the 2.5-min initial nonreinforced period of training sessions 15 or 16, or failed to meet the criterion of acquiring the discrimination at 60% correct lever responding during the sessions. The mean discrimination performance based on percent correct lever responding in sessions 15 and 16 for the remaining 24 animals was 83.93 (±2.45 SEM). Based on this discrimination performance, animals were matched and randomly assigned to one of two chronic treatment groups. Mean percent correct lever responding for the resulting groups was 84.58 (±3.36 SEM) and 83.39 (±3.64 SEM).

Chronic treatment. Prior to chronic drug treatment, the animals were tested in one 2.5-min nonreinforced test session following the administration of 0.00625 mg/kg quinpirole. Two animals were discontinued from the study at this point because they failed to respond at least five times during the test session. The mean percent quinpirole lever responding for the two groups was 38.94 (±.07 SEM) and 40.43 (±9.30 SEM). The chronic treatment groups received daily SC injections of either 1 mg/kg spiperone (n = 11) or distilled water (n = 10) for 10 consecutive days. No testing or retraining was conducted during this chronic treatment period.

Rebound testing. Twenty-four hours after the conclusion of the chronic treatment regimen, animals were tested for rebound-produced sensitization. All animals were administered 0.00625 mg/kg quinpirole 20 min before a 2.5-min nonreinforced test session.

Results and Discussion

Six animals failed to meet the more-than-five-responses criterion during the postchronic treatment test session. Data from these animals are excluded from the results. Recalculation of mean percent quinpirole lever responding in the prechronic treatment test excluding these animals yielded means of 41.19 (±9.51 SEM) for the spiperone treatment group (n = 7), and 38.98 (±10.95 SEM) for the distilled water treatment group (n = 9). Following chronic treatment, the mean percent quinpirole lever responding for the spiperone treatment group was 34.28 (±7.39 SEM) and for the distilled water treatment group was 48.51 (±9.59 SEM). There were no main effects of chronic treatment group [$F(1, 14) = 0.232$, $p = 0.638$], or pre- vs. posttreatment test measure [$F(1, 14) = 0.159$, $p = 0.696$]. The predicted interaction between these variables was not significant [$F(1, 14) = 1.936$, $p = 0.186$]. Chronic spiperone treatment did not enhance quinpirole-appropriate lever responding.

Given our previous reports of increased amphetamine-appropriate lever responding following chronic haloperidol treatment (2,3,10), the failure to observe antagonist-induced rebound effects in Experiments 2 and 3 was unexpected. One explanation is that, at the time of testing, sufficient time had not elapsed for the antagonists to have cleared. In fact, although not significant, in all cases the groups tested following

chronic antagonists made fewer responses on the quinpirole lever than the water-treated control animals, which suggested blockade rather than sensitization of the quinpirole cue. Although, as seen in Fig. 4 of Experiment 1, after 24 h, 0.02 mg/kg of spiperone no longer blocked the quinpirole cue, the dose of spiperone used during the 10 days of chronic treatment was greater by a factor of 50—i.e., 1.0 mg/kg. Thus, observation of chronic antagonist-induced sensitization to the quinpirole cue might require longer posttreatment-test intervals using the specific antagonists and doses employed in these experiments. An independent assessment of the effects of chronic treatment at longer intervals could not be done by additional tests with the same animals because the initial test involved a challenge dose of the agonist.

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