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A Lever-Release Version of the Conditioned Avoidance Response Paradigm: Effects of Haloperidol, Clozapine, Sulpiride, and BMY-14802

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WHITE, I. M., M. T. CIANCONE, J. L. HARACZ AND G. V. REBEC. *A lever-release version of the conditioned avoidance response paradigm: Effects of haloperidol, clozapine, sulpiride, and BMY-14802.* PHARMACOL BIOCHEM BEHAV **41**(1) 29–35, 1992.—Rats trained on a lever-release version of the conditioned avoidance response (CAR) task were used to test the behavioral effects of established and putative antipsychotic drugs. Baseline CAR latencies decreased as the conditioned-unconditioned stimulus interval was shortened from 500 to 250 ms. Haloperidol, clozapine, and BMY-14802 decreased successful avoidance responses and increased avoidance latencies in a dose-dependent manner without affecting the latency of escape responses. In contrast, sulpiride failed to affect either successful avoidance response rates or avoidance latency. Sulpiride, however, significantly attenuated d-amphetamine-induced locomotion and rearing compared to vehicle-treated controls. Similar effects of these antipsychotics have been reported on shuttlebox avoidance, and these results now are confirmed in a CAR paradigm that achieves greater control over behavior. Because this paradigm elicits a discrete forelimb response without activating numerous muscle groups, it is potentially useful as a tool for examining neuronal mechanisms underlying the behavioral effects of antipsychotic drugs.

Amphetamine BMY-14802 Clozapine Conditioned avoidance response Haloperidol Lever release Stereotypy Sulpiride

THE conditioned avodance response (CAR) task, in which an animal must respond to a conditioned stimulus (CS) in order to avoid an aversive event, has become a useful behavioral screen in the development of antipsychotic drugs (4,5). These drugs disrupt CAR performance at doses that correlate closely with their antipsychotic potency (1,16). This disruption presumably reflects a blockade of dopamine transmission since CAR performance requires an intact dopaminergic projection to the forebrain (14) and virtually all antipsychotics are known to block D2 dopamine receptors in various forebrain regions (3,18).

In most versions of the CAR task, rats learn to avoid footshock by moving from one shuttlebox compartment to another during presentation of a CS that is often compound in nature (e.g., light and tone). The prolonged CS typically elicits long-latency (≥5 s) locomotor avoidance responses, which involve numerous neural systems and muscle groups. Although effective for screening new antipsychotic drugs, this avoidance paradigm is not well suited for studying underlying neural substrates. Such an analysis is best carried out with procedures that evoke a limited set of movements mediated by a relatively small group of neural circuits (12,36). This requirement has been met in a modified version of the CAR task, in which a brief, auditory CS elicits a discrete, short-latency motor response. In this paradigm, rats are trained to perform a CAR consisting of a lever release shortly after CS onset in order to avoid footshock (20, 27, 35). This task elicits a rapid forelimb response without requiring activation of numerous muscle groups, thus simplifying the underlying neural circuitry.

The lever-release CAR task also is extremely responsive to changes in dopamine transmission. A unilateral dopamine loss in the neostriatum of only 15%, for example, is sufficient to impair performance on this task (28). Performance also is affected by slight, natural variations in neostriatal dopamine-receptor density (35). Thus, to the extent that antipsychotics interfere with dopamine transmission, the lever-release CAR task should provide a sensitive index of antipsychotic drug-induced behavioral effects.

In this study, we tested several drugs on the lever-release CAR task as a basis for subsequent research on the neural mechanisms underlying antipsychotic drug-induced behavioral effects. We assessed the effects of both classical and atypical antipsychotic drugs, including haloperidol, a nonselective dopamine antagonist, and clozapine, an atypical antipsychotic with a broad range of action on several neurotransmitter systems. We

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also tested sulpiride, a selective D2 antagonist, and BMY-14802, a recently developed sigma ligand that may represent a new generation of antipsychotic agents (26,30). Sulpiride also was tested for its ability to reverse amphetamine-induced behavioral responses in an open-field situation.

METHOD

Subjects

A total of 65 male, Sprague-Dawley rats, weighing between 300–400 g at the start of the experiment, served as subjects. All animals were housed individually under standard laboratory conditions and were maintained on a 12-h light/dark cycle with light on at 0700.

Drugs

Haloperidol HCl (McNeil), clozapine (Sandoz), (−)-sulpiride HCl (RBI), (±)-sulpiride HCl (RBI), and BMY-14802 (Bristol Myers) were mixed in a solution of 5% tartaric acid. d-Amphetamine sulfate (Sigma) was mixed in 0.9% saline and expressed as the free base. Doses of all other drugs were expressed as the salt. All drugs tested on CAR were administered intraperitoneally (IP). d-Amphetamine was administered subcutaneously (SC).

CAR Apparatus

Animals were tested on the level-release CAR task in an operant chamber (25 × 30 cm with a height of 35 cm). A sound generator (Cutler-Hammer), which delivered the auditory stimulus (96 dB click), was mounted 10 cm above the chamber. Eighteen grid bars on the floor of the chamber were connected to a neon grid scrambler (Lafayette, model 58020) and a shock generator (Lafayette, model 82400). The operant chamber and auditory-stimulus generator were placed in a sound-attenuating box equipped with a houselight (7.5 W). A lever, 4.5 cm by 2.5 cm, was mounted 6.5 cm above the chamber floor.

Delivery of both the auditory stimulus and the footshock (2 mA, square wave, 1-s maximum duration) was controlled by an IBM-XT compatible computer (PC limited) via an interface board. Behavioral output information (the presence or absence of the response as well as its latency) was sent to the computer and recorded automatically [see (17)].

CAR Procedure

Initially, subjects were trained by successive approximations to depress the lever with a forepaw to escape footshock. Animals learned this response within 10–20 min. Once this response was learned, animals received the auditory CS followed by footshock, which served as the unconditioned stimulus (US). To avoid the shock, animals were required to make a rapid forepaw withdrawal response during the CS-US interval (interstimulus interval, ISI). The number of trials was increased gradually over 5 sessions from 25 to 50 trials per session. Only one training session was administered per day. The time between trials (intertrial interval, ITI) was 12–15 s. If an animal did not depress the lever during the ITI, a brief shock was administered 3–5 seconds after the ITI. This always induced animals to press the lever. These inducing shocks were rarely given, however, because most trained animals depressed the lever within a few seconds of release.

All subjects were trained with an ISI of 500 ms. When they

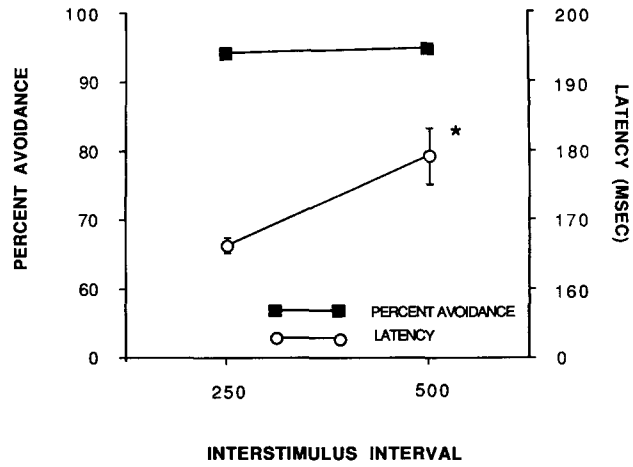

FIG. 1. Effect of interstimulus interval (ISI) on percent avoidance and average avoidance latency during baseline testing. In this and other figures, brackets represent the SEM [$p<0.02$: 500 ms ISI (n = 10) vs. 250 ms ISI (n = 10)]. An asterisk denotes a significant difference between the 250 and 500 ms ISI conditions.

were able to avoid shock at least 80% of the time for 5 or more consecutive sessions, the animals were ready to begin the drug phase. Ten to 15 sessions were required to reach this criterion. Some animals were trained further to achieve the same rate of avoidance at an ISI of 250 ms before the drug phase began.

During the drug phase, which spanned several weeks, subjects received (IP) either haloperidol (0.00, 0.01, 0.05, 0.10, 0.25, and 0.50 mg/kg), clozapine (0.00, 0.5, 1.0, 2.5, and 5.0 mg/kg). (−)-Sulpiride (0.00, 0.5, 1.0, 2.5, 5.0, and 20.0 mg/kg), (±)-sulpiride (0.00, 50.0, and 100.0 mg/kg), or BMY-14802 (0.00, 1.0, 2.5, 5.0, and 10.0 mg/kg). A dose of 0.00 mg/kg indicates the vehicle injection. Doses were administered in counterbalanced order. At least 4 days elapsed between drug injections to prevent cumulative drug effects. On a drug-test day, subjects received 50 predrug trials. If performance was 80% or better, subjects received a single drug injection. Thirty min after injection, a total of 50 postdrug trials was given. Before the next drug-test day, animals were required to perform at least three 80%-successful nondrug sessions. In some cases, an animal was tested with more than one drug, but when this occurred, a 4–6-week recovery period (no drugs, no training) intervened before subsequent retraining and drug testing. During each drug trial, we monitored successful avoidance rate and the latency of the avoidance response (i.e., time to release the lever following CS onset). On unsuccessful trials, we calculated escape latency (i.e., time to release the lever after US onset).

To facilitate group comparisons, data were expressed as the drug-induced percent change in performance from the baseline session immediately before drug injection. Change in percent avoidance [100% × (number of successful avoidances/total number of trials)] was expressed as either a decrease or an increase following drug administration compared to the baseline. Avoidance latency was calculated by averaging the latencies of all successful avoidance responses in a given session. Percent change in avoidance latency [100% × ([postdrug avoidance latency − baseline avoidance latency]/baseline avoidance latency)] also was calculated. These results were analyzed with a one-way repeated measures analysis of variance (ANOVA), followed by post hoc comparisons performed with the Bonferroni method. To mini-

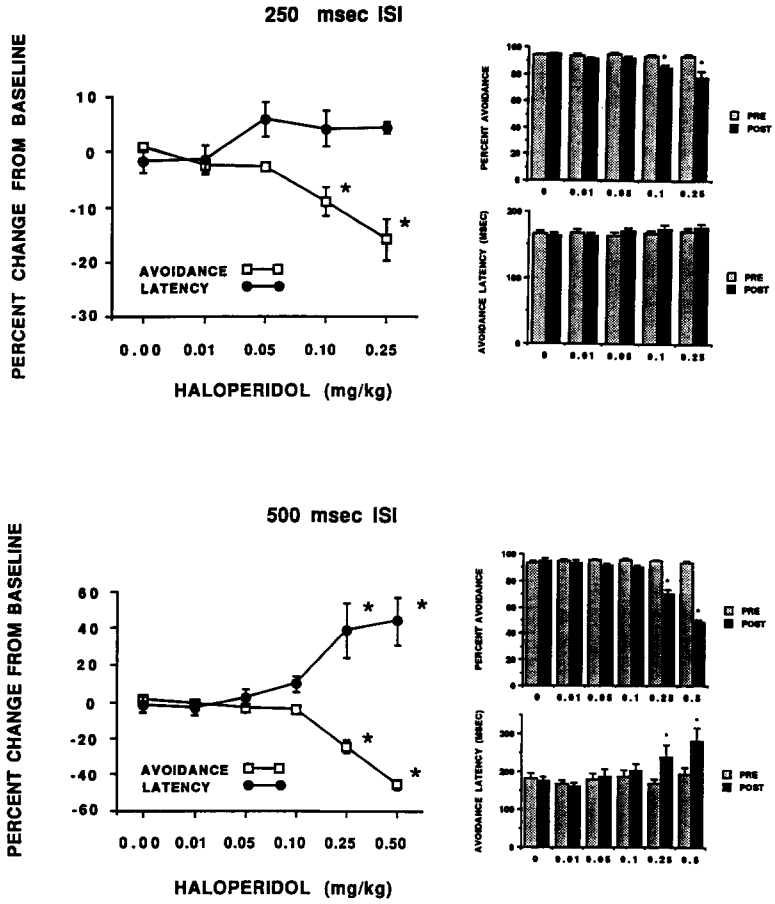

FIG. 2. Effect of haloperidol (0.01–0.50 mg/kg, IP) on percent avoidance and percent avoidance latency at 250 ms (top; n = 10) and 500 ms (bottom; n = 10) ISI. Values are expressed as percent change from baseline. Overall group differences were tested by using repeated measures ANOVAs ($p<0.001$). The mean percent avoidance and avoidance latencies (ms) during pre- and postdrug trials are depicted in the graphs on the right. Asterisks denote significant differences compared to the vehicle-treated control group after a Bonferroni post hoc comparison (top: $p<0.005$; bottom: $p<0.003$).

mize session variability, the first 10 trials during the pre- and postdrug sessions were not included for analysis.

Amphetamine-Induced Behavioral Response

Animals were placed individually in wire-bottomed, Plexiglas observation chambers (32 × 32 cm with a height of 35 cm) and housed overnight under standard laboratory conditions. On the following day, the animals received (IP) either 20.0 mg/kg (−)-sulpiride, 50.0 or 100.0 mg/kg (±)-sulpiride, or vehicle followed 10 min later by 1.0 mg/kg d-amphetamine (SC). All animals were used only once. Behavior was observed continuously for 2-min intervals between 10 to 70 min after amphetamine administration. Individual items of behavior, including locomotion, rearing, sniffing, and repetitive head movements, were rated according to their intensity (0 = not present, 1 = mild, 2 = moderate, 3 = extreme) and duration (1 = discontinuous, 2 = continuous) during each 2-min interval. These ratings, which were multiplied to yield a single value (e.g., the maximum score at each interval was 6), are sensitive to changes in the amphetamine-induced behavioral response produced by antipsychotic drugs (23,29). Average scores per 2-min interval were analyzed with a one-way ANOVA and Tukey HSD post hoc comparison.

RESULTS

Effect of ISI and Haloperidol on CAR

Rats were trained with an ISI of either 500 or 250 ms and then challenged with haloperidol (0.01–0.50 mg/kg). Baseline percent avoidance was approximately 94% at both ISIs. The latency of avoidance responses, however, differed significantly with ISI, $F(1,9) = 8.66$, $p<0.02$: the shortest ISI produced the shortest latency responses (Fig. 1). Haloperidol produced a significant dose-dependent decline in successful avoidances at an ISI of either 500, $F(5,45) = 115.44$, $p<0.001$, or 250 ms, $F(4,36) = 9.56$, $p<0.001$ (Fig. 2). Pairwise comparisons with vehicle injections revealed a significant effect of the two highest doses tested at either ISI. A significant increase in avoidance latency, however, occurred only at the longest ISI, $F(5,45) = 9.39$,

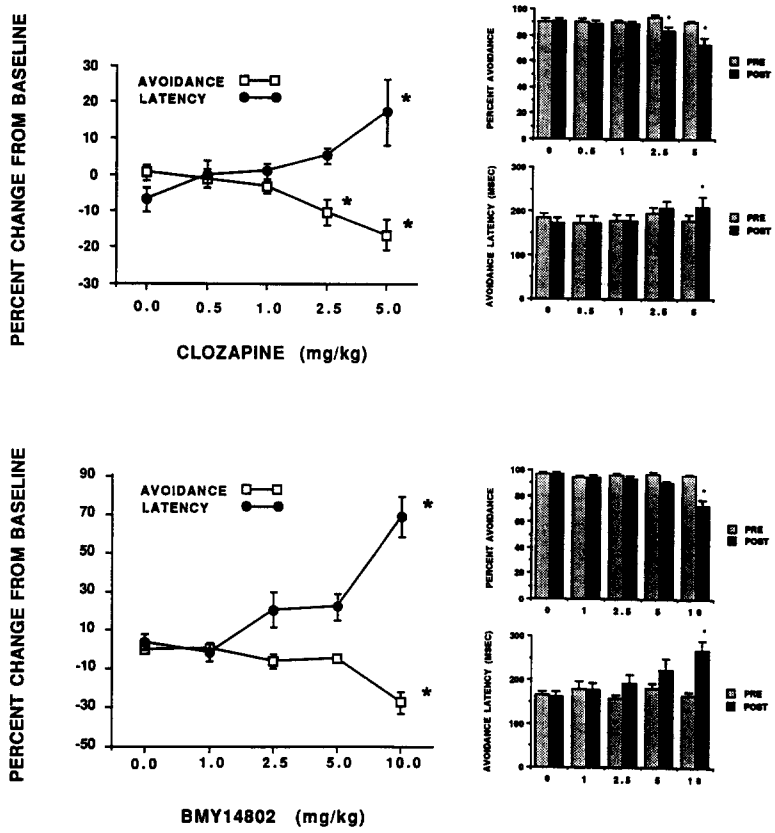

FIG. 3. Effect of clozapine, (0.5–5.0 mg/kg; n = 6) and BMY-14802 (1.0–10.0 mg/kg; n = 7) on percent avoidance and percent avoidance latency at 500 ms ISI. Values are expressed as percent change from baseline. Overall group differences were tested by using repeated-measures ANOVAs (see the Results section for details). The mean percent avoidance and avoidance latencies (ms) during pre- and postdrug trials are depicted in the graphs on the right. Asterisks denote significant differences compared to the vehicle-treated control group after a Bonferroni post hoc comparison ($p<0.005$).

$p<0.001$, and pairwise comparisons indicated a significant effect of 0.25 and 0.50 mg/kg compared to vehicle.

Doses of haloperidol that produced a significant increase in avoidance latency (0.25 and 0.50 mg/kg) failed to alter the latency of escape responses. Escape latencies at these doses typically ranged between 50 and 65 ms, which were similar to baseline values (49 to 69 ms). In both baseline and haloperidol-treatment conditions, rats reliably escaped shock on trials with avoidance failures, $t(18) = -0.28$, $p>0.05$ for 0.25 mg/kg; $t(18) = 0.97$, $p>0.05$ for 0.50 mg/kg.

Effect of Clozapine and BMY-14802 on CAR

Like haloperidol, clozapine and BMY-14802 lowered the percentage and increased the latency of successful avoidance responses at an ISI of 500 ms (Fig. 3). Clozapine (0.5–5.0 mg/kg) produced a significant dose-dependent decrease in percent successful avoidance, $F(4,20) = 8.59$, $p<0.001$, and a significant increase in latency, $F(4,20) = 3.27$, $p<0.05$. Post hoc comparisons showed that compared to vehicle injections, both 2.5 and 5.0 mg/kg clozapine significantly impaired avoidance rate, whereas only the highest dose significantly affected latency. BMY-14802 (1.0–10.0 mg/kg) produced comparable changes in avoidance rate, $F(4,24) = 11.47$, $p<0.001$, and latency, $F(4,24) = 16.71$, $p<0.001$. Pairwise comparisons with vehicle injections revealed a significant effect of the highest dose of BMY-14802 on both measures. Like haloperidol, however, neither clozapine, $t(10) = 0.48$, $p>0.05$ for 2.5 mg/kg; $t(10) = -0.33$, $p>0.05$ for 5.0 mg/kg, nor BMY-14802, $t(12) = 0.67$, $p>0.05$, altered escape latency.

Effect of Sulpride on CAR

(−)-Sulpiride (0.5–20.0 mg/kg) failed to alter either percent avoidance, $F(5,25) = 1.62$, $p>0.05$, or response latency, $F(5,25) = 0.93$, $p>0.05$, nor was there a trend toward a change even at the highest dose tested (Fig. 4). These measures were similarly unaffected by (±)-sulpiride, though at a dose of 100 mg/kg avoidance responding became highly variable (Fig. 4). At this dose, the majority of animals draped themselves across the lever with eyes closed and showed a marked lack of spontaneous movement between trials. Neither (−)- nor (±)-sulpiride altered escape rates and latencies [e.g., mean escape latencies for baseline and 100 mg/kg (±)-sulpiride conditions were 54 and 64 ms, respectively]. Because it has been reported that sulpiride impairs CAR performance gradually, peaking at 4 to 6 h after injection

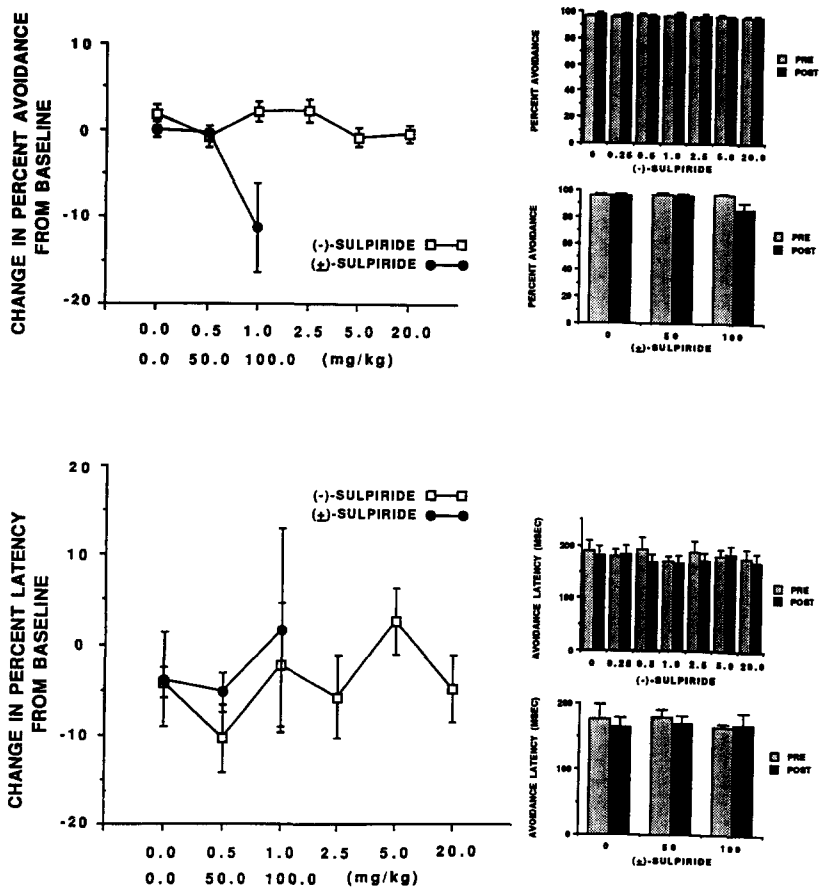

FIG. 4. Effect of (−)-sulpiride (0.5–20.0 mg/kg; n = 6) and (±)-sulpiride (50.0 and 100.0 mg/kg; n = 6) on percent avoidance and percent avoidance latency at 500 ms ISI. Values are expressed as percent change from baseline. The mean percent avoidance (top) and avoidance latencies (bottom) during pre- and postdrug trials are depicted in the graphs on the right. Repeated-measures ANOVAs revealed no significant differences.

(1), we tested 4 animals at 4 h after administration of 50.0 mg/kg (±)-sulpiride. Under these conditions, neither avoidance rate, $t(6) = -0.56$, $p > 0.05$, nor latency, $t(6) = -0.35$, $p > 0.05$, was affected.

Sulpiride-Induced Changes in the Behavioral Response to Amphetamine

Because of the lack of a consistent effect of either (−)- or (±)-sulpiride on CAR performance, we assessed the ability of these drugs to block the open-field behavioral response to 1.0 mg/kg d-amphetamine. Ratings of individual behaviors revealed that all doses tested [20.0 mg/kg (−)-sulpiride; 50.0 and 100.0 mg/kg (±)-sulpiride] significantly reduced amphetamine-induced locomotion, $F(3,31) = 14.66$, $p < 0.001$, and rearing, $F(3,31) = 10.78$, $p < 0.001$, compared to vehicle-treated controls (Fig. 5). In addition, ANOVAs showed overall group differences in sniffing, $F(3,31) = 6.40$, $p < 0.002$, and repetitive head movements, $F(3,31) = 3.65$, $p < 0.025$. Post hoc Tukey HSD revealed that 100.0 mg/kg (±)-sulpiride significantly attenuated sniffing, but did not affect repetitive head bobbing behavior. After we omitted the 100.0 mg/kg (±)-sulpiride group because of its variability, the overall group differences in head movements remained significant, $F(2,24) = 7.49$, $p < 0.003$, and post hoc comparisons revealed that 50.0 mg/kg (±)-sulpiride and 20.0 mg/kg (−)-sulpiride significantly blocked amphetamine-induced repetitive head bobbing.

DISCUSSION

Our results confirm and extend evidence that both classical and atypical neuroloptics impair CAR performance. Consistent with data obtained from other avoidance paradigms (1, 2, 13, 16, 24, 25, 30, 32), haloperidol, clozapine, and BMY-14802 produced significant dose-dependent reductions in the percentage of successful avoidance responses on the lever-release task. Moreover, doses that impaired CAR performance failed to alter escape latency, arguing against a simple sedative effect of these drugs on behavior. This result is consistent with previous findings that doses of haloperidol and clozapine selectively impaired avoidances without disrupting escape responses (1, 6, 9). Although a low dose of haloperidol (0.03 μg/rat) has been shown to attenuate step-through passive avoidance without affecting locomotion (15), the potency of haloperidol in our lever-release

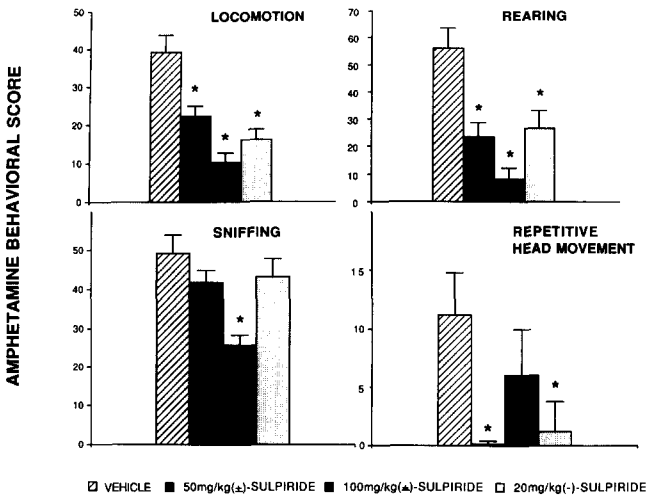

FIG. 5. Effect of (−)-sulpiride (20.0 mg/kg; n=9) and (±)-sulpiride (50.0 and 100.0 mg/kg; n=8–9) on d-amphetamine-induced locomotion, rearing, sniffing, and repetitive head movement. Values are presented as the total mean score for each behavior between 10–70 min after amphetamine administration (see the Method section for details). Overall group differences were tested by one-way ANOVA (see the Results section for details). Asterisks denote significant differences compared to vehicle-treated control group after Tukey HSD post hoc comparisons ($p<0.05$).

task is comparable to this drug's potency in shuttlebox avoidance tasks (1,37). Interestingly, however, haloperidol, clozapine, and BMY-14802 significantly increased avoidance latency, which may indicate subtle motor impairments, including drug-induced postural adjustments in initiating a lever-release response (11). Such impairments, if they occurred, did not alter escape latencies, suggesting that motor capacity was adequate to the task demands of our experiment. Our findings of an increase in avoidance latency, therefore, suggests a drug-induced impairment specifically related to the performance of the learned response. This result may reflect the antipsychotic action of haloperidol and clozapine and may serve as the predictor of such an action of BMY-14802.

Our baseline ISI data indicate that the lever-release response did not reflect a nonspecific startle reaction to the CS alone. In fact, 3 animals whose ISI was changed from 500 to 1000 ms increased their response latency by as much as 300 ms (unpublished observations). An increase in response latency with an increase in ISI indicates that animals are learning to release the lever in sufficient time to avoid shock rather than reacting to the CS alone. Moreover, a startle response should not decline during extinction, yet preliminary data show a significant decline to CS-alone trials, which is apparent as early as the first day of such testing (unpublished observations). It also is noteworthy that the lever-release version of the CAR task is especially sensitive to impairments in dopamine transmission. Thus a 15% reduction in neostriatal dopamine is sufficient to impair lever-release CAR (28), whereas dopamine depletions up to 90% fail to disrupt startle (7).

Sulpiride failed to impair lever-release avoidance, even at doses that significantly decreased the behavioral response to amphetamine. Thus the inactivity of sulpiride in the CAR task did not result from an insufficient amount of drug to influence behavior. In fact, our findings, including the nonsignificant trend toward CAR impairment after the highest (±)-sulpiride dose, parallel previous data on this drug (10, 16, 19, 32). If effective at all in these studies, high-dose sulpiride usually produced only modest impairments in shuttlebox or lever-press CAR performance. When injected centrally, however, sulpiride reliably impairs CAR performance, particularly when the injections are aimed at the nucleus accumbens (22,33). This finding, coupled with evidence that sulpiride-induced CAR impairments do not peak until several hours after systemic injection (1,22), suggests that sulpiride has difficulty crossing the blood-brain barrier. Although this explanation could account for the inability of sulpiride to alter performance on our lever-release task, it is important to note that we also found sulpiride to be ineffective in a preliminary study of animals tested as late as 4 h after injection. Similarly, Nakajima and McKenzie (21) found no effect of systemic sulpiride on rewarding brain stimulation following a similar postinjection interval. It also is noteworthy that systemic sulpiride impaired amphetamine-induced behaviors within minutes after administration, suggesting that prolonged delays are not always necessary in order to observe a behavioral response to this D2 antagonist. Moreover, not all amphetamine-induced behaviors were suppressed equieffectively by sulpiride, arguing against a simple sedative effect of this drug on behavior. Presumably, systemic sulpiride produces effects that prevent antagonism of lever-release CAR behavior. Such antagonism may be found after sulpiride injections in nucleus accumbens or possibly other areas.

The ability of BMY-14802 to impair lever-release CAR behavior supports evidence for a potential antipsychotic role for this and possibly other sigma antagonists (26,31). Although haloperidol shares a high affinity for the sigma site, this mechanism alone cannot explain the ability of antipsychotic drugs to impair CAR performance because clozapine, a relatively weak sigma ligand, also blocks CAR behavior (8). It seems likely, therefore, that this behavior is influenced by several neurochemical mechanisms, all of which regulate neostriatal function.

Further analysis of CAR behavior requires an examination of its neuronal substrates of CAR performance to the lever-release task, implicate this task as a potentially useful tool for such an analysis. This conclusion is supported by our preliminary recordings of neostriatal single-unit responses related to the CS or the lever release in rats performing our version of the CAR task (34). Testing the responses of these neurons to clinically effective antipsychotic drugs during lever-release CAR performance promises to shed a new light on the neuronal mechanisms underlying the behavioral effects of these drugs.

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REFERENCES

1. Arnt, J. Pharmacological specificity of conditioned avoidance response inhibition in rats: inhibition by neuroleptics and correlation to dopamine receptor blockade. Acta Pharmacol. Toxicol. 51:321–329; 1982.

2. Bloss, J. L.; Singer, G. H. Neuropharmacological and behavioral evaluation of prostaglandin E2 and 11-thiol-11-desoxy prostaglandin E2 in the mouse and rat. Psychopharmacology (Berlin) 57:295–302; 1978.

3. Carlsson, A. Antipsychotic drugs, neurotransmitters, and schizophrenia. Am. J. Psychiatry 135:164–173; 1978.
4. Cook, L.; Weidley, E. Behavioral effects of some psychopharmacological agents. Ann. NY Acd. Sci. 66:740–752; 1957.
5. Costall, B.; Naylor, R. J. Assessment of the test procedures used to analyze neuroleptic action. Rev. Pure Appl. Pharmacol. Sci. 1:3–83; 1980.
6. Davidson, A. B.; Weidley, E. Differential effects of neuroleptic and other psychotropic agents on acquisition of avoidance in rats. Life Sci. 18:1279–1284; 1976.
7. Davis, M. Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm. Behav. Neurosci. 100:814–824; 1986.
8. Ferris, R. M.; Tang, F. L. M.; Chang, K.-J.; Russell, A. Evidence that the potential antipsychotic agent rimcazole (BW234U) is a specific, competitive antagonist of sigma sites in brain. Life Sci. 38: 2329–2337; 1986.
9. Fibiger, H. C.; Zis, A. P.; Phillips, A. B. Haloperidol-induced disruption of conditioned avoidance responding: attenuation by prior training or by anticholinergic drugs. Eur. J. Pharmacol. 30:309–314; 1975.
10. Fontaine, O.; Libon, Ph.; Richelle, M. Action of a new psychotropic drug (sulpiride) on avoidance behavior in rats. Psychopharmacologia 39:309–314; 1974.
11. Fowler, C.; Ford, K. E.; Gramling, S. E.; Nail, G. L. Acute and subchronic effects of neuroleptics on quantitative measures of discriminative motor control in rats. Psychopharmacology (Berlin) 84: 368–373; 1984.
12. Gormezano, I.; Kehoe, E. J.; Marshall, B. S. Twenty years of classical conditioning with the rabbit. Prog. Psychobiol. Physiol. Psychol. 10:197–274; 1983.
13. Hillegaart, V.; Ahlenius, S.; Magnusson, O.; Fowler, C. J. Repeated testing of rats markedly enhances the duration of effects induced by haloperidol on treadmill locomotion, catalepsy, and a conditioned avoidance response. Pharmacol. Biochem. Behav. 27: 159–164; 1987.
14. Koob, G. F.; Simon, H.; Herman, J. P.; LeMoal, M. Neuroleptic-like disruption of the conditioned avoidance response requires destruction of both the mesolimbic and nigrostriatal dopamine systems. Brain Res. 303:319–329; 1984.
15. Kovacs, G. L.; De Wied, D. Effects of amphetamine and haloperidol on avoidance behavior and exploratory activity. Eur. J. Pharmacol. 53:103–107; 1978.
16. Kuribara, H.; Tadokoro, S. Correlation between antiavoidance activities of antipsychotic drugs in rats and daily clinical doses. Pharmacol. Biochem. Behav. 14:181–192; 1981.
17. Lavond, D. G.; Steinmetz, J. E. An inexpensive interface for the IBM PC/XT and compatibles. Behav. Res Methods Instrum. Comput. 21:435–440; 1989.
18. Leysen, J. E.; Janssen, P. A. Specificity of ligands used in psychiatric research. In: Sen, A. K.; Lee, T., eds. Receptors and ligands in psychiatry. Cambridge: Cambridge University Press; 1988:526–543.
19. Ljungberg, T. Blockade by neuroleptics of water intake and operant responding for water in the rat: ahedonia, motor deficit, or both? Pharmacol. Biochem. Behav. 27:341–350; 1987.
20. MacRae, P. B.; Spirduso, W. W.; Wilcox, R. E. Reaction time and nigrostriatal dopamine function: the effects of age and practice. Brain Res. 451:139–148; 1988.
21. Nakajima, S.; McKenzie, G. Reduction of the rewarding effect of brain stimulation by a blockade of dopamine D1 receptor with SCH23390. Pharmacol. Biochem. Behav. 24:919–923; 1986.
22. Nishibe, Y.; Matsuo, Y.; Yoshizaki, T.; Eigyo, M.; Shiomi, T. Hirose, K. Differential effects of sulpiride and metoclopramide on brain homovanillic acid levels and shuttlebox avoidance after systemic and intracerebral administration. Naunyn Schmiedebergs Arch. Pharmacol. 321:190–194; 1982.
23. Rebec, G. V.; Pierson, E. E.; McPherson, F. A.; Brugge, K. Differential sensitivity to amphetamine following long-term treatment with clozapine or haloperidol. Psychopharmacology (Berlin) 77: 360–366; 1982.
24. Sanger, D. J. The effect of clozapine on shuttle-box avoidance responding in rats: Comparison with haloperidol and chlorodiazapoxide. Pharmacol. Biochem. Behav. 23:231–236; 1985.
25. Sanger, D. J. Response decrement patterns after neuroleptic and non-neuroleptic drugs. Psychopharmacology (Berlin) 89:98–104; 1986.
26. Snyder, S. H.; Largent, B. L. Receptor mechanisms in antipsychotic drug action: focus on sigma receptors. J. Neuropsychiatry 1:7–15; 1989.
27. Spirduso, W. W.; Farrar, R. P. Effects of aerobic training on reactive capacity: an animal model. J. Gerontol. 36:654–662; 1981.
28. Spirduso, W. W.; Gilliam, P. E.; Schallert, T.; Upchurch, M.; Vaughn, D. M.; Wilcox, R. E. Reactive capacity: a sensitive behavioral marker of movement initiation and nigrostriatal dopamine function. Brain Res. 335:45–54; 1985.
29. Tschanz, J. T.; Rebec, G. V. Atypical antipsychotic drugs block selective components of amphetamine-induced stereotypy. Pharmacol. Biochem. Behav. 31:519–522; 1988.
30. Taylor, D. P.; Dekleva, J. Potential antipsychotic BMY-14802 selectively bind to sigma sites. Drug Dev. Res. 11:65–70; 1987.
31. Taylor, D. P.; Eison, M. S.; Moon, S. L.; Yocca, F. D. BMY-14802: a potential antipsychotic with selective affinity of σ-binding sites. In: Tamminga, C. A.; Schulz, S. C., eds. Advances in neuropsychiatry and psychopharmacology, vol. I: Schizophrenia research. New York: Raven Press; 1991:307–315.
32. Usuda, S.; Nishikori, K.; Noshiro, O.; Maeno, H. Neuroleptic properties of cis-N-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (YM-09151-2) with selective antidopaminergic activity. Psychopharmacology (Berlin) 73:103–109; 1981.
33. Wadenberg, M.-L.; Ericson, E.; Magnusson, O.; Ahlenius, S. Suppression of conditioned avoidance behavior by the local application of (−)-sulpiride into the ventral, but not the dorsal, striatum of the rat. Biol. Psychiatry 28:297–307; 1990.
34. White, I. M.; Haracz, J. L.; Langley, P. E.; Ciancone, M. T.; Rebec, G. V. Dopamine- and sigma-receptor antagonists impair reaction-time conditioned avoidance responding in rats. Soc. Neurosci. Abstr. 16:132; 1990.
35. Wolf, M. D.; Wilcox, R. E.; Riffee, W. H.; Abraham, L. D. Strain differences in dopamine receptor function and the initiation of movement. Pharmacol. Biochem. Behav. 13:5–7; 1980.
36. Woody, C. D. Understanding the cellular basis of memory and learning. Ann. Rev. Psychol. 37:433–493; 1986.
37. Worms, P.; Brockkamp, C. L. E.; Lloyd, K. G. Behavioral effects of neuroleptics. In: Coyle, J. T.; Enna, S. J., eds. Neuroleptics: Neurochemical, behavioral and clinical perspectives. New York: Raven Press; 1983:93–117.