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Effects of Corticotropin Releasing Factor, Desipramine and Haloperidol on a DRL Schedule of Reinforcement[1]

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BRITTON, K. T. AND G. F. KOOB. *Effects of corticotropin releasing factor, desipramine and haloperidol on a DRL schedule of reinforcement.* PHARMACOL BIOCHEM BEHAV **32**(4) 967–970, 1989.—Rats were trained on a schedule of differential-reinforcement-of-low-rate (DRL) which has been proposed to be differentially sensitive to antidepressant drugs. Desipramine and haloperidol decreased response rate and increased reinforcement rate. CRF decreased response rate and failed to change reinforcement rate. Amphetamine produced the opposite pattern of increased response rate and decreased reinforcement rate. These results question the specificity of the DRL task as a screen for antidepressants and suggest that drugs that moderately lower response rate may produce a behavioral profile on this task similar to that of tricyclic antidepressants.

CRF Desipramine Haloperidol DRL schedule of reinforcement

SEIDEN and co-workers have demonstrated that a variety of tricyclic antidepressants, monoamine oxidase inhibitors and some atypical antidepressants produce characteristic changes in responding on a schedule of reinforcement that rewards long pauses between responses for water (3–7, 11, 12). Rats trained on this reinforcement schedule, a differential-reinforcement-of-low-rate (DRL), are required to inhibit responding for a minimum specified period of time in order to obtain a reward. The duration that Seiden *et al.* have found to be most effective requires a long pause between responses of 72 sec. Seiden *et al.* have proposed that such a DRL schedule provides a test that is differentially sensitive to the effects of antidepressant compounds.

Recently, however, Pollard and Howard (2,8) have presented data that question the specificity of the DRL schedule as a screen for antidepressants. They have found that, while the test accurately identifies a variety of antidepressants, it fails to identify atypical antidepressants with stimulant properties in rats (nomofensine and buproprion) and falsely identifies the antipsychotic compounds chlorpromazine and haloperidol.

The purpose of the current investigation was to examine further the pharmacological specificity of action of antidepressants on DRL responding. We examined the effects of the peptide, corticotropin releasing factor (CRF) and the psychostimulant amphetamine on DRL responding as well as the action of the antipsychotic haloperidol. CRF injected intracerebroventricularly (ICV) has motor activating effects in photocell cages (13) and can augment behavioral responses to stressful environments (13).

METHOD

Subjects

The subjects were male Wistar albino rats weighing 200–250 g at the beginning of the experiment. The rats were housed in groups of three per cage in a temperature-, humidity- and light-controlled environment (lights on 0700 hr; lights off 1900 hr; temperature: 72–78°F; humidity 50–55%). For DRL testing rats were deprived initially to 85% of their free feeding weight and then maintained on 21 g of food per day in addition to that earned during testing. The animals had ad lib access to water in the home cage. The animals continued to gain weight and by the end of the testing one year later, weighed 543±14 grams (mean±SEM).

DRL Training

Soundproof operant chambers, each equipped with a lever and dispenser for obtaining 45 mg food pellets were used. Ten rats were initially trained under a continuous reinforcement schedule and, after earning 100 food pellets, transferred to a DRL 10 sec schedule for 10 weeks. The interresponse time was gradually advanced to 20 sec (over 4 weeks)

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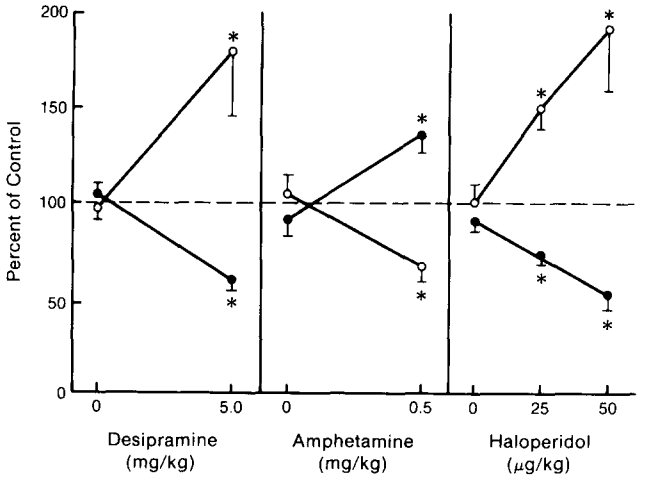

FIG. 1. Effect of desipramine, amphetamine and haloperidol on responses (closed circles) and reinforcements (open circles) per 1-hr session on a DRL 60-sec schedule. N=10 except for haloperidol (25 and 50 μg/kg) where N=9. *Significantly different from baseline control value, paired t-test, $p<0.05$.

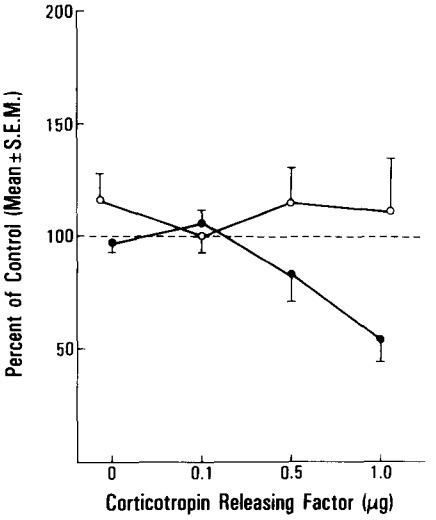

FIG. 2. Effect of CRF on responses (closed circles) and reinforcements (open circles) per 1-hr session on a DRL 60-sec schedule. N=10 at each point (mean±SEM). *Significantly different from saline control, Newman-Keuls test following a significant ANOVA, $p<0.05$.

TABLE 1

EFFICIENCY RATIOS ON A DRL 60-SECOND SCHEDULE

	Efficiency Ratio (mean ± S.E.M.)
Saline	21.4 ± 3.6
DMI (5 mg/kg)	51.5 ± 6.5*
Saline	33.1 ± 7.7
Amphetamine (0.5 mg/kg)	14.2 ± 3.2*
Saline	27.4 ± 5.2
Haloperidol (25 μg/kg)	46.9 ± 5.7*
Saline	24.1 ± 5.5
Haloperidol (50 μg/kg)	59.0 ± 4.7*
Saline	28.3 ± 5.1
CRF (0.1μg ICV)	26.4 ± 3.6
CRF (0.5 μg ICV)	40.7 ± 5.0
CRF (1.0 μg ICV)	53.9 ± 8.2†

*$p<0.05$ paired t-test; †$p<0.05$ Newman-Keuls test.

and finally to 60 sec (over 12 weeks) in subsequent sessions. Responses that occurred at least 60 sec after the previous response were reinforced, whereas responses that occurred less than 60 sec after the previous response were not reinforced. Subjects were then trained in daily 1 hour sessions five days/week until stable baseline responding was obtained (12 weeks). Stability was defined as no change greater than 10% of the mean for all ten rats on any given day for three consecutive days including a saline injection.

Surgery

Rats were anesthetized with pentobarbital (50 mg/kg) and a 7 mm 23-gauge stainless steel guide cannula was lowered within 1 mm of the lateral ventricle and secured with two stainless steel screws and dental cement. The stereotaxic coordinates, with the toothbar 5 mm above interaural zero, were: −0.6 mm posterior to bregma, ±2.0 mm lateral, and −3.2 mm below the skull surface at the point of entry. Cannulas were equally distributed between left and right ventricles. Rats were allowed at least two days to recover from surgery before resuming baseline testing.

TABLE 2

INTERRESPONSE TIME DISTRIBUTIONS IN 3 SEC BINS†

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Saline (IP)	9.5	1.2	3.1	5.0	7.5	9.1	9.8	8.9	7.6	6.8	5.5	3.1	2.6	1.5	1.2	0.7	0.5	0.4	0.4	0.9
DMI	2.6*	0.6	0.2	1.6	2.4*	4.1*	3.8*	4.6*	4.6*	4.2	4.8	4.1	2.3	2.9*	1.1	1.8*	1.4	0.6	0.6	4.5*
Saline (SC)	5.0	1.7	1.1	3.0	5.9	9.4	9.3	8.7	9.3	5.8	3.8	2.4	1.1	1.6	1.3	1.0	0.6	0.9	0.7	1.8
Haloperidol (50 μg)	2.4*	0.7	0.8	1.4	1.9*	1.7*	2.3*	2.7*	2.8*	2.4*	3.8	3.0	2.2	2.3	1.3	2.1*	0.9	0.8	1.0	6.3*
Saline (ICV)	7.2	1.3	2.8	4.9	6.3	8.0	8.6	7.6	7.2	5.5	6.0	4.8	3.0	1.8	1.4	0.7	1.1	0.5	0.1	0.9
CRF (1 μg)	7.8	1.0	1.2	1.4	1.8*	2.2*	2.6*	2.2*	2.5*	2.5	2.3*	1.8*	2.1	1.0	1.1	1.2	0.6	0.3	0.7	5.9*

*$p<0.05$ paired test.

†Values represent mean responses per 3-sec bin of 10 rats except for haloperidol which represents 9 rats. Bin 20 includes all values over 58 sec.

Drug Administration

Rat CRF (J. Rivier, The Salk Institute) was dissolved in saline and administered ICV by gravity 1 hr prior to testing. Previous extensive work in our laboratory has shown that all cannulas with good flow are patent following dye injections. No problems with flow were encountered with these animals. Injectable haloperidol (injection provides 5 mg haloperidol [as the lactate] with 1.8 mg methylparaben and 0.2 mg propylparaben per ml and lactic acid for pH adjustment between 3.0–3.6) and amphetamine were dissolved in saline and administered subcutaneously (SC), 30 min prior to testing. Desipramine was dissolved in saline and was administered intraperitoneally 1 hr prior to testing. During dose-response testing, each animal received each dose of the drug in ascending order. Injections were given no more frequently than one every 7 days. Saline injections were administered on the day prior to drug testing for the systemic injections and on two days prior to drug testing for each ICV injection. All of the drug treatments were given to each rat including the ICV CRF. The order of drug treatments was DMI (5 mg/kg), CRF (0.1 μg ICV), CRF (1.0 μg ICV), haloperidol (25 μg/kg), haloperidol (50 μg/kg), and amphetamine (0.5 mg/kg).

Data Analysis

Total number of responses and reinforcements for 10 rats were recorded for each 1 hour session (n=9 for haloperidol experiments due to equipment problem in one chamber). Baseline control values were obtained from the mean values for the three days preceding the saline and drug testing. The number of responses and reinforcements per session at each drug dose were analyzed for statistically significant differences from baseline control values with paired t-tests using a two-tailed criterion of statistical significance. For the CRF dose-response test, the percent changes between treatment and the average of 2 preceding baseline days were subjected to an analysis of variance; the zero dose was calculated using the very first saline injection prior to 0.1 μg CRF test. Post hoc testing was conducted using the Newman-Keuls, a posteriori test.

RESULTS

The mean baseline response and reinforcements per session were 81.1±5.2 (range: 66.7–124.0) and 17.8±3.0 (range: 8.3–24.3), respectively.

Analysis of DRL responding in desipramine-, CRF-, amphetamine- and haloperidol-treated animals revealed significantly different patterns of responses and reinforcements. Desipramine decreased responses, $t(9)=4.34$, $p<0.05$, and concomitantly increased reinforcements, $t(9)=2.62$, $p<0.05$. Haloperidol produced quantitatively similar effects on both responding [i.e., decreased, 25 μg: $t(8)=7.02$; 50 μg: $t(9)=5.53$, $p<0.05$] and reinforcements [i.e., increased, 25 μg: $t(8)=3.63$; 50 μg: $t(8)=3.23$, $p<0.05$], see Fig. 1. CRF also reduced responding, $F(3,27)=5.76$, $p<0.05$, but failed to significantly increase reinforcements ($F<1$), see Fig. 2.

Desipramine, haloperidol and CRF also had similar effects on responding based on two other measures. All three treatments significantly increased the efficiency of responding on the schedule (number of reinforcers earned per session divided by number of responses), see Table 1, whereas amphetamine significantly decreased efficiency. Also, analysis of the interresponse time distributions showed that all three treatments that increased efficiency effectively flattened the IRT distributions compared to the appropriate saline controls, see Table 2. Analysis of variance revealed significant treatment × time interactions for each treatment (ANOVAs; CRF treatment × bin interaction, $F(19,171)=4.98$, $p<0.05$; Haloperidol treatment × bin interaction, $F(19,152)=9.07$, $p<0.05$; DMI treatment × bin interaction, $F(19,171)=6.87$, $p<0.05$, and individual means comparisons using a paired t-test revealed a significant increase in the longest IRT bin (20) for DMI, haloperidol and CRF. Under the saline condition, responding peaked during bins 1, 6, 7, 8 and 9. For the treatments peaks were generally shifted to later bins 9, 10, 11 and 20.

DISCUSSION

An analysis of the results in terms of response and reinforcer frequency shows that desipramine decreased the number of responses and increased the number of reinforcers obtained on a DRL task with a long interresponse time. Haloperidol and CRF produced qualitatively the same effects on response and frequency as desipramine. However, CRF did not increase significantly the number of reinforcers obtained. Similar results, however, were observed with all three treatments on reinforcement efficiency where desipramine, haloperidol and CRF significantly increased efficiency. Also all three flattened the IRT distribution and produced longer IRTs. In contrast, the effects of amphetamine on performance under the DRL 60-sec schedule were qualitatively different; amphetamine increased response rate and decreased reinforcer rate; an effect well documented by Schuster and colleagues (9,10). These results fail to confirm the specificity of the DRL task as a screening test for identification of antidepressant drugs and support the contention that any treatment that produces a moderate reduction in response rate is likely to increase reinforcement efficiency (8).

Our findings are very similar to those recently reported by Pollard and Howard (8) where they showed that treatments that reduce responses, but which do not interfere with the physical capacity to respond, tend to increase reinforcement efficiency. Our results agree with their finding that antipsychotic compounds produce effects qualitatively similar to imipramine.

CRF is a peptide with psychostimulant effects as well as stress enhancing actions (13) that reduces responding in a number of operant paradigms [(1), unpublished results]. Similar rate-suppressing effects were observed in the current study, but no significant increase in reinforcement frequency was obtained. The degree of the response suppression at the highest dose, however was of sufficient magnitude to produce an increase in reinforcement efficiency.

In summary, the DRL 60-sec test correctly identified the antidepressant desipramine, but failed to reject the antipsychotic haloperidol. The neuropeptide CRF produced decreased response rate and no change in reinforcement rate. These data do not completely agree with the results of Seiden *et al.* (12) but replicate similar effects observed by Pollard and Howard (8). In addition, the data suggest that treatments such as haloperidol that reduce responses moderately are likely to increase reinforcement frequency (8). While it is clear that the DRL test is very sensitive to tricyclic antidepressants (12), our results suggest that the DRL task lacks some selectivity as a primary screening method for antidepressant treatments.

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