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BRIEF COMMUNICATION

Use of DRL in Differentiating Anxiolytic and Neuroleptic Properties of CNS Drugs[1]

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CANON, J. G. AND A. S. LIPPA. *Use of DRL in differentiating anxiolytic and neuroleptic properties of CNS drugs.* PHARMAC. BIOCHEM. BEHAV. 6(5) 591–593, 1977. – Presented in this paper are the effects of chlorpromazine, clozapine, d-amphetamine and diazepam on DRL behavior in rats. D-Amphetamine and diazepam, which showed similar effects on response errors, could be identified on the basis of burst responding and drug interaction. Clozapine, a new antipsychotic agent which does not cause extrapyramidal side effects in man, affected DRL behavior in the same way as did chlorpromazine. Thus, DRL schedules are probably not useful in differentiating various neuroleptic agents.

DRL Burst responding Drug interaction d-Amphetamine Diazepam Chlorpromazine Clozapine

THE EFFECT of drugs on temporal discrimination has been a useful behavioral research tool in central nervous system (CNS) drug research for many years. One of the most useful procedures employed for such investigations has been the differential reinforcement of low rates (DRL) procedure. This reinforcement schedule requires that responses must be withheld for a certain length of time in order for the response to be rewarded [9]. Several classes of CNS drugs have been known to disrupt performance under DRL schedules [1, 3, 5, 6]. Recently, Sanger and Blackman have shown that the anxiolytic drug chlordiazepoxide (CDPD) increased burst responding (i.e., responses with an inter-response time, IRT, less than 1.5 sec) in a DRL schedule much more consistently than did d-amphetamine (d-AMPH) [8]. Prior to this report, the effects of CDPD and d-AMPH on DRL performance could not be differentiated. One goal of the present experiments was to further explore the effects of the anxiolytic diazepam (DIAZ) upon burst responding. A secondary purpose of the present work was to determine the behavioral profile of clozapine (CLOZ), a novel neuroleptic, on DRL performance.

METHOD

Animals

Twelve male albino rats (Wistar, Royalhart Farms) served as the test animals. They weighed approximately 250 g at the start of the experiment.

Apparatus

The apparatus consisted of four standard Gerbrands (Model C) operant test chambers with one lever centered on the metal wall 3-1/4 in. from the grid floor. A pellet dispenser, when activated, released a single Noyes food pellet (0.045 g) into the food receptacle.

Procedure

The DRL 10 sec schedule specified a 10 sec holding period during which all bar press responses must be withheld by the animal subject to ensure access to reinforcement. Premature responses (those occurring less than 10 sec since the last response) reset the clock and started a new 10 sec holding period. All rats received forty

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sessions under a DRL 10 sec schedule before drug testing was started. Stability criterion was based on the change in response rate (excluding responses with latencies less than 1 sec) and rewards (pellets) to be $\leq 10\%$ of the 3-session predrug mean.

The drugs and doses used in these experiments were as follows: d-amphetamine sulfate (d-AMPH) 0.5 and 1 mg/kg; diazepam hydrochloride (DIAZ) 5 and 10 mg/kg; clozapine (CLOZ) 5 and 10 mg/kg; and chlorpromazine hydrochloride (CPZ) 2.5 and 5 mg/kg. d-AMPH was dissolved in sterile mammalian Ringers solution and administered IP, 30 min before testing. The other drugs were mixed or dissolved in a universal solution which consisted of 2% starch, 0.5% PEG (polyethleneglycol) and 1 drop TWEEN-80 per 10 ml solution. For CLOZ 0.1 N HCl was added initially to dissolve the drug, DIAZ, CLOZ and CPZ were administered orally, 60 min before testing.

The experiments were controlled using a PDP-8 computer (Digital Equipment Corporation) – SKED Language System [10]. All response data were collected by the computer and printed out on a teletype at the end of each session.

RESULTS

In Fig. 1 the effects of CPZ, CLOZ, DIAZ, and d-AMPH on DRL behavior are shown as a function of percent change from control. Three measures of DRL behavior are examined (i.e., bursts – responses emitted less than 1.0 sec apart, errors – responses emitted between 1.0 to 9.9 sec since the last response, and reinforcements – pellets rewarded by a bar press with an interresponse time of 10 or more sec). General effects can be noted. On burst behavior only DIAZ (10 mg/kg) showed a significant ($p<0.01$) change from control. Although d-AMPH (1.0 mg/kg) increased burst responding only two of 11 rats as compared to eight of 11 rats for DIAZ (10 mg/kg) increased their burst responses by 75 or more responses over the control mean (42 ± 24 bursts). Both CPZ and CLOZ significantly ($p<0.05$) reduced bar press errors at the higher dose level. The number of reinforcements (pellets) were lowered significantly for both d-AMPH (0.5 and 1.0 mg/kg) and DIAZ (10 mg/kg).

In a second set of experiments the effects of drug interactions were studied on response rate in the DRL 10 sec schedule. Animals were given combinations of either d-AMPH and CPZ, d-AMPH and CLOZ or CLOZ and DIAZ. The results are shown in Fig. 2. d-AMPH (1.0 mg/kg) when combined with either CLOZ (5.0 mg/kg) or CPZ (2.5 mg/kg) increased response rate 28% and 34%, respectively, over that seen after d-AMPH alone. The depressant effects on response rate produced by the higher doses of CPZ and CLOZ were reversed by d-AMPH. This seemingly biphasic action of CPZ on d-AMPH has previously been reported [2,4]. In contrast the administration of DIAZ did not increase response rate at the low dose of CLOZ nor reverse its depressant effects. Instead it further potentiated the response decrement especially in conjunction with the high dose of CLOZ (10 mg/kg).

DISCUSSION

The results of this study suggest the possibility that different classes of psychotropic drugs may be differentiated on the basis of their effects on DRL performance. Both CPZ and CLOZ depressed the number of errors committed at the higher dose level. d-AMPH and DIAZ reduced the number of reinforcements but only DIAZ

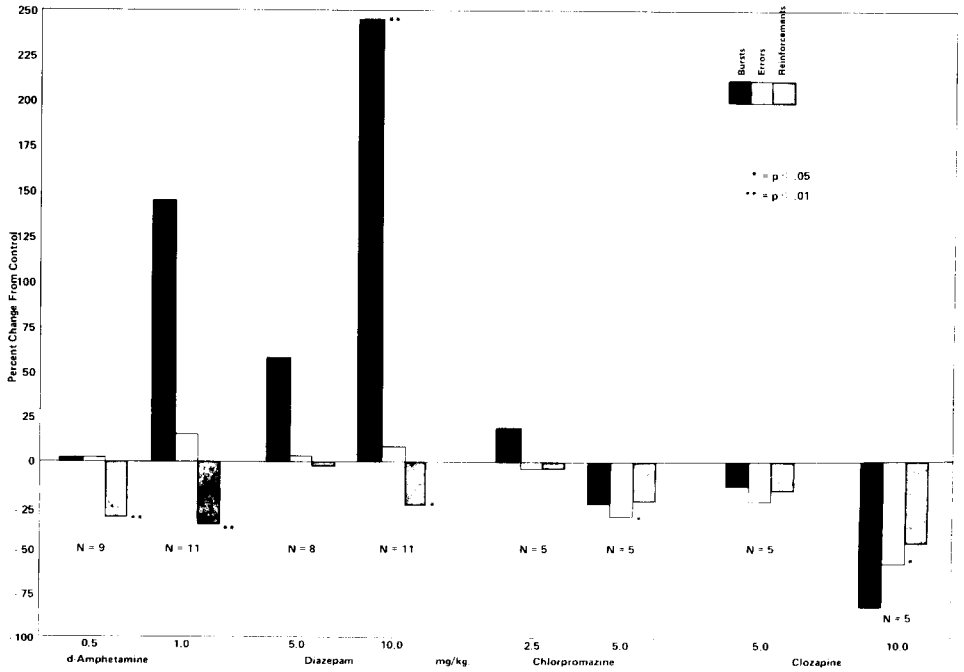

FIG. 1. Bar-graphs of percent change from control for bursts (black), errors (white) and reinforcements (gray) on animals under a DRL 10 sec schedule. All drug doses given in mg/kg. Probability levels made between control and drug sessions using a two-tailed dependent t-test.

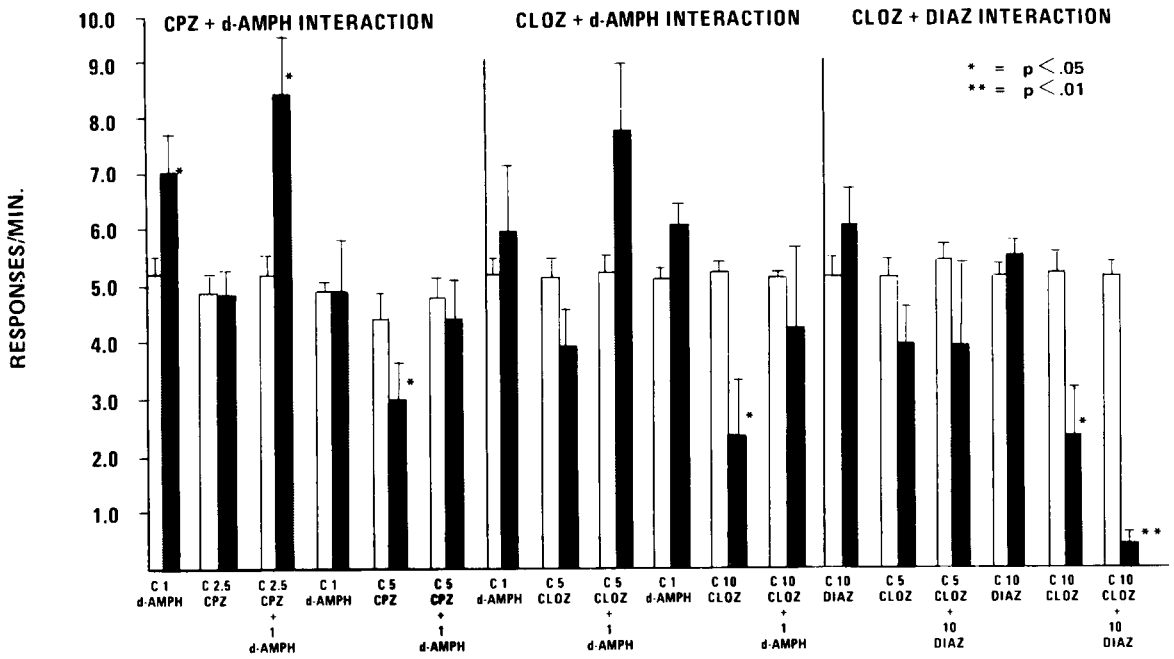

FIG. 2. Bar-graphs of mean rate of responding on a DRL 10 sec schedule under control (C) and drug conditions. All drug doses given in mg/kg. Each bar represents the mean of five animals except the CLOZ (10) + d-AMPH (1) interaction experiment where N = 4. Probability levels made between control and drug sessions using a two-tailed dependent *t*-test. The vertical lines atop the bar graphs represent standard errors of the mean.

showed a consistent effect on burst responses. It has previously been reported [7,8] that CDPD produces a consistent effect on response bursts. Other compounds used in the treatment of anxiety have also been shown to increase burst responding [3,8]. CLOZ, a new antipsychotic with low extrapyramidal side effect liability, demonstrated virtually no behavioral differences from CPZ at the doses tested. To further explore possible differences or similarities between the two neuroleptics, as well as d-AMPH and DIAZ, interaction experiments were carried out using the DRL 10 sec. paradigm. Both CLOZ and CPZ when combined with d-AMPH showed similar profiles; a potentiation of the d-AMPH effect at the lower doses while at the higher doses the reverse was seen (i.e., a block of the response depression produced by CPZ and CLOZ). CLOZ (10 mg/kg) when interacted with DIAZ (10 mg/kg) produced only response depression. This result suggests another means of differentiating the effects of d-AMPH and DIAZ upon DRL performance.

In conclusion, the results of these initial studies illustrate the potential utility of the DRL procedure for classifying psychotropic drugs according to their therapeutic activity. Antipsychotic drugs would be expected to reduce errors and interact with d-AMPH in a competitive manner. Anxiolytics, on the other hand, would be expected to decrease reinforcements, increase burst responding and not competitively interact with antipsychotics. Stimulants would be expected to decrease reinforcements and competitively interact with antipsychotics. Additional testing, however, is required to firmly establish the selectivity of this procedure.

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