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BRIEF COMMUNICATION

An Efficient Chronic Conflict Paradigm: Lick Suppression by Incremental Footshock

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McCOWN, T. J., R. A. VOGEL AND G. R. BREESE. *An efficient chronic conflict paradigm: Lick suppression by incremental footshock.* PHARMACOL BIOCHEM BEHAV **18**(2) 277–279, 1983.—A conflict paradigm was designed which uses water as the reinforcer and incremental footshock as the punishment. It is easy to initiate responding and to maintain stable baselines over long periods of time. This paradigm proved selective for clinically effective anxiolytic compounds while a number of psychotropic compounds, which have no clinical anxiolytic activity, were not effective.

Chronic conflict paradigm Lick suppression Incremental footshock

DURING the past twenty years, the rat approach-avoidance paradigm, or conflict model, introduced by Geller and Seifter [3], has proven a selective screening test for antianxiety drugs. There is a high positive correlation with clinically effective anxiolytic drugs for both clinical potency and effectiveness [1]. The typical Geller-Seifter paradigm utilizes a two-part operant schedule where rats receive food reinforcements for lever presses under a variable interval (VI) schedule followed by a period of continuous reinforcement (CRF) where each reinforcement is paired with footshock. This punished period of responding results in varying levels of response suppression, depending upon the shock intensity, whereas the unpunished segment provides a within-subject control for any drug impairment of performance. It was found that anxiolytic compounds, such as the benzodiazepines, uniquely increased responding during the punished segment, but had no effect upon responding during the unpunished segment. Non-anxiolytic compounds which altered punished responding also altered unpunished responding. Over the years a number of alterations in the basic paradigm have been introduced, most notably the use of incremental shock levels, instead of fixed shock levels [5] and the use of water as a reinforcer, instead of food [7]. The present conflict paradigm combines water reinforcement and incremental shock to produce a conflict paradigm which is easy to initiate and to maintain over long periods of time.

METHOD

All subjects were naive male Sprague-Dawley rats (Charles River Laboratories, Somerville, MA) weighing between 250–300 grams at the beginning of the experiments. They had ad lib access to food and were maintained on a 12 hour (0700–1900 hr) light-dark cycle. All testing occurred during the light phase. The apparatus consisted of standard rodent operant chambers from Colburn Instruments (Lehigh Valley, PA) fitted with water bottles which were connected to a drinkometer circuit. All contingencies were controlled and responses recorded by a PDP-8L computer.

Initially, the rats were deprived of water 24 hours prior to the first day of training. The first 3 days of training and acclimation to the test apparatus consisted of placing the subjects into the operant chambers and allowing each animal to drink freely for 10 minutes. Immediately following the test each animal received 30 minutes of water ad lib. This amount of access to water sustained a suitable level of deprivation, yet the weight gain over the period of experiments was similar to that of naive rats. The animals were then placed on a multiple operant schedule consisting of a 5 min period of unpunished licking (CRF) followed by a 2.5 minute punished period where every 20th lick (FR20) resulted in a footshock (BSR, LVE Model SGS-004). The current intensity began at 0.01 mA and increased by 0.01 mA every subsequent shock. Each subject completed two of these cycles each day over the next week. At this time the punished schedule was reduced to an FR5. This schedule produced a level of response suppression which was amenable to experimental manipulation such that both increases and decreases in responding could be observed. Additionally, the unpunished period was reduced to 3 minutes and the punished period to 2 minutes, with each subject completing two cycles for a total test time of 10 minutes per subject. From one to two weeks of testing were required to stabilize responding.

The drugs tested were chosen from a number of clinically active anxiolytic compounds which included chlordiazepoxide, diazepam, flunitrazepam, and pentobarbital, as well as a wide range of psychotropic drugs with no clinical anxiolytic activity including amphetamine, chlorpromazine,

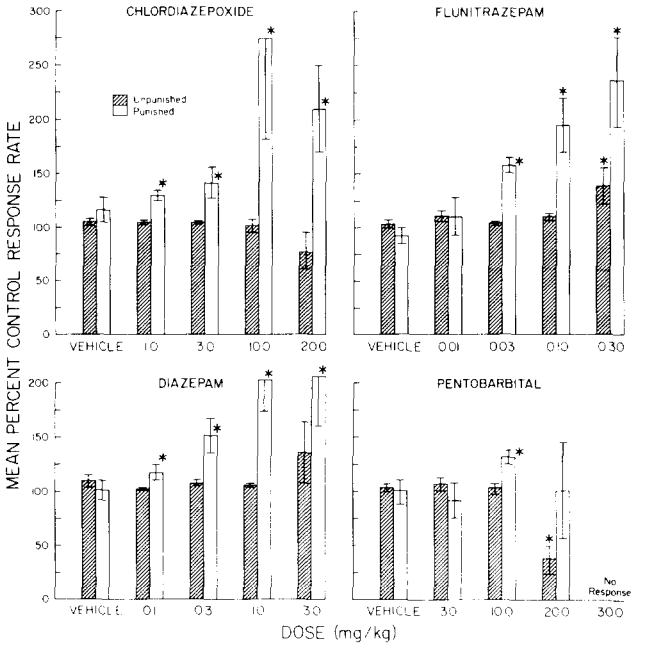

FIG. 1. The effects of several anxiolytic drugs on punished and unpunished responding for water by rats. Each animal received the indicated dose of chlordiazepoxide, flunitrazepam, diazepam, or pentobarbital 30 min prior to testing (at least 5 subjects per dose). Each test session consisted of two cycles, with each cycle having a 3 min unpunished period followed by a 2 min FR5 punished period. *$p<0.05$ compared to the control baseline using a two-tailed t-test for differences between means of dependent samples [4].

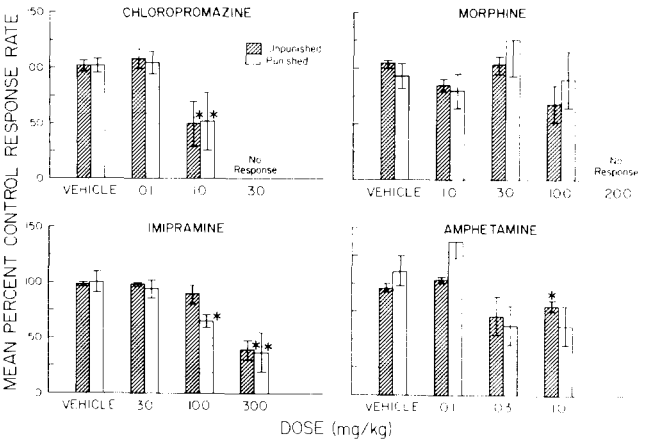

FIG. 2. The effects of several psychotropic drugs on punished and unpunished responding for water by rats. Each animal received the indicated dose of chlorpromazine, morphine, imipramine, or d-amphetamine 30 min prior to testing (at least 5 subjects per dose). Each test session consisted of two cycles, with each cycle having a 3 min unpunished period followed by a 2 min FR5 punished period. *$p<0.05$ compared to the control baseline using a two-tailed t-test for differences between means of dependent samples [4].

imipramine, and morphine. All drugs were dissolved in saline except flunitrazepam and diazepam, which were suspended in 0.5% methylcellulose, and were injected intraperitoneally (IP) 30 min prior to testing. The drugs were administered in a randomized order, and all but two subjects were tested under each drug category. Following each drug test approximately 3 to 4 days were allowed for reestablishing a stable baseline response.

RESULTS

Through the use of water reinforcement and incremental footshock punishment, training and baseline stabilization were easily accomplished over a three week period. During this period of training and baseline stabilization, it was found that either more rapid increments in the level of shock, or a decrease in the fixed ratio resulted in a greater suppression of responding during the punished period. By using 0.01 mA increments in current intensity and an FR5 schedule during the punished period, the level of responding was suitable to observe either increases or decreases in responding (average=80 rsp/2.5 min period).

Figure 1 shows that the classic anxiolytic compounds chlordiazepoxide, flunitrazepam and diazepam cause a significant dose-related increase in punished responding while having no effect on unpunished drinking. This antipunishment action roughly parallels the clinical potency of these drugs with diazepam being 10 times more potent and flunitrazepam 100 times more potent than chlordiazepoxide. Pentobarbital, which has been used clinically as an anxiolytic [1], provided a small but significant increase in punished responding at one dose (10.0 mg/kg) whereas higher doses only caused decreases in both punished and unpunished responding. These data indicate that the paradigm, like many other variations of the conflict task or Geller-Seifter paradigm, is relatively selective for drugs exhibiting anxiolytic properties.

Figure 2 provides dose-response data for four compounds which clinically do not have anxiolytic activity. As seen in Fig. 2, chlorpromazine, morphine, imipramine and amphetamine do not increase punished responding. Although amphetamine and imipramine have significant effects on unpunished responding and punished responding respectively, the general trend for these drugs, as well as for chlorpromazine, is a decrease in responding. For the highest doses of chlorpromazine (3.0 mg/kg) and morphine (20.0 mg/kg) the subjects did not respond at all.

DISCUSSION

The basic Geller-Seifter conflict model was introduced over twenty years ago [3]; however, some difficulties were recognized as utilization of the paradigm expanded. The shock intensity had to be gradually adjusted over time for each subject in order to maintain a stable level of suppression. Also, it is common practice to continually evaluate the performance of subjects treated with chordiazepoxide, excluding the non-responders [6]. By using incremental shock intensities, the subjects self-titrate the level of shock in each session [5] making the level of punished responding stable. The use of water reinforcement contributes to a short training period [2]. When the incremental shock is combined with water reinforcement, excellent drug selectivity is achieved in a naive group of subjects using short testing sessions.

It is possible that the observed increase in punished drink-

ing following benzodiazepine treatment might be due to a drug-induced increase in thirst. However, it was found that doses of chlordiazepoxide which caused significant increases in punished drinking did not significantly alter drinking over a twenty minute period.

Since subjects in this paradigm can be easily maintained for at least five months, the cost of running chronic studies is minimized. Additionally, this paradigm provides a useful vehicle to study the mechanisms responsible for the anti-conflict action of the anxiolytic drugs.

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REFERENCES

1. Cook, L. and J. Sepinwall. Behavioral analysis of the effects and mechanisms of action of benzodiazepines. In: *Mechanism of Action of Benzodiazepines*, edited by E. Costa and P. Greengard. New York: Raven Press, 1975, pp. 1–28.
2. Ford, R. D., R. H. Rech, R. L. Commissaris and L. Y. Meyer. Effects of acute and chronic interactions of diazepam and d-amphetamine on punished behavior of rats. *Psychopharmacology* **65:** 197–204, 1979.
3. Geller, I. and J. Seifter. The effects of meprobamate, barbiturates, d-amphetamine and promazine on experimentally induced conflict in the rat. *Psychopharmacologia* **1:** 482–492, 1960.
4. Glass, G. V. and J. C. Stanley. *Statistical Methods in Education and Psychology*. Englewood Cliffs, NJ: Prentice Hall, 1970, pp. 297–300.
5. Pollard, G. T. and J. Howard. The Geller-Seifter conflict paradigm with incremental shock. *Psychopharmacology (Berlin)* **62:** 117–121, 1979.
6. T'so, T. O. T. and M. B. Chenoweth. Comparison between chronic chlordiazepoxide treatment and shock removal in a conflict situation in rats. *Neuropharmacology* **15:** 99–101, 1976.
7. Vogel, J. R., B. Beer and D. E. Clody. A simple and reliable conflict procedure for testing anti-anxiety agents. *Psychopharmacologia* **21:** 1–7, 1971.