Pharmacology Biochemistry and Behavior, Vol. 2, pp. 465–472. ANKHO International Inc., 1974. Printed in the U.S.A.

Schedule-Dependent Differences Among Anti-Anxiety Drugs

PAUL W. WEDEKING

Department of Pharmacology, The Squibb Institute for Medical Research, Princeton, New Jersey 08540

(Received 28 November 1973)

WEDEKING, P. W. *Schedule-dependent differences among anti-anxiety drugs.* PHARMAC. BIOCHEM. BEHAV. 2(4) 465–472, 1974. – Five anti-anxiety drugs were administered to rats on either a variable-interval (VI 1-min) schedule, a chained 10-sec differential reinforcement of other behavior (DRO), fixed-ratio (FR 25) procedure, or an FR 15-satiation schedule. Two dose levels, free of effects on behavior not related to lever pressing, for each anxiolytic were selected for testing. On the VI schedule, the anti-anxiety drugs uniformly increased response rates. On the DRO-FR procedure all the anxiolytics increased responding during the DRO component, but produced dissimilar biphasic increases or decreases in FR response rates. The anti-anxiety drugs also produced dissimilar effects on the FR-satiation schedule: chlordiazepoxide, phenobarbital, and meprobamate disrupted satiation (increased responding), diazepam did not affect satiation (no change in responding), and oxazepam facilitated satiation (decreased responding). None of the anxiolytics altered FR response rates in the FR-satiation schedule. The discrepancies recorded suggest that schedule-dependent differences exist between the anti-anxiety drugs studied.

Anti-anxiety drugs Benzodiazepines Disinhibition Differential reinforcement of other behavior Fixed-ratio Meprobamate Phenobarbital Satiation Variable-interval

THERE have been a number of explanations for the effects that chlordiazepoxide and other anti-anxiety drugs have on food-reinforced behavior. In 1962, Richelle and co-workers [19] reported that chlordiazepoxide, when administered to rats trained on a fixed-interval schedule or a differential reinforcement of low rates (DRL) schedule, increased responding in both schedules. The disruptions were attributed to an interference with temporal discriminations produced by the muscle-relaxant effect of chlordiazepoxide.

In a study of various psychotropic drugs, Bainbridge [1] reported that anti-anxiety drugs (chlordiazepoxide, meprobamate, and phenobarbital) increased the number of lever presses made by rats conditioned on a fixed-ratio (FR) schedule. The increased responding was attributed to controlling fear.

Surveying the effects that minor tranquilizers have on rats in diverse behavioral procedures, Margules and Stein [14] proposed a theory of disinhibition to explain the effects that anxiolytic agents have on suppressed behavior. They suggested that anti-anxiety drugs increased the rate of occurrence of previously suppressed behavior by releasing that behavior from inhibition.

Recently, Miczek [16] reported that rats trained on either a concurrent variable-interval (VI) food-reinforced, FR punishment schedule or a multiple VI reinforcement and concurrent reinforcement-and-punishment, time-out (S^{Δ}) schedule found that chlordiazepoxide did not affect non-punished of S^{Δ} responding but did increase responding during the reinforced-and-punishment contingencies. Miczek attributed his findings to the observation that chlordiazepoxide attenuated "effectively and specifically the suppressive effects of punishment."

Although chlordiazepoxide has been widely investigated in many behavioral procedures, other anti-anxiety drugs have not been studied for their effects on behavior maintained by food-reinforcement schedules not involving foot-shock punishment, even though it has been suggested that anxiolytics produce the same activity in a specific behavioral schedule [10,14].

To further investigate the effects of anti-anxiety drugs on behavior in food-reinforced schedules, this report describes the effects that administering chlordiazepoxide, diazepam, oxazepam, meprobamate, and phenobarbital have on the performance of rats conditioned in either a VI 1-min schedule, a chained 10-sec differential reinforcement of other behavior (DRO), FR 25 procedure (DRO-FR), or an FR 15-satiation schedule (cf. 21). The anti-anxiety drugs were selected as being representative of the clinically utilized class of anti-anxiety drugs [10,11,12]. The three schedules were selected for their ability to maintain lever-pressing at high rates (FR components of the schedules), moderate rates (VI schedule), and low rates (engendered by the response inhibiting contingency of the DRO component). The FR-satiation procedure was used to elucidate any effects that the anti-anxiety drugs had on the motivation for food and on satiation [21] since anti-anxiety drugs are reported to increase eating behavior [1, 8, 12, 14, 18].

METHOD

Four Lehigh Valley Electronics operant chambers (No. 143-21) were isolated in ventilated, light- and sound-attenuated enclosures. A rat lever (BRS/LVE No. 121-105) was mounted in each chamber with a white light (S^{D}) mounted 5 cm above the lever. Each reinforcement was a

single 45-mg Noyes food pellet. The schedules were controlled by electromechanical equipment located in an adjacent room, a cumulative record was made of each session.

Experiment 1: VI 1-min Schedule

The VI 1-min schedule was utilized for maintaining a continuous emission of lever-presses by the rat [4]. To start the session, the house light was extinguished and the S^D turned on; at random intervals (10–110 sec without associated stimuli) a lever press was reinforced by delivery of a food pellet. Each rat performed for 60 min each day and at the end of the session, the S^D was extinguished and the house light was lit. Water was available ad lib during the session. Two behavioral indices were tabulated: total number of lever-presses and total number of reinforcements obtained during each session.

Experiment 2: Chained 10-sec DRO, FR 25 Schedule

The DRO-FR procedure was used to study the effects that drugs have on FR responding and on the low levels of lever pressing engendered by DRO. The DRO was used in preference to an S^Δ component to permit evaluation of the effects of anti-anxiety drugs on a programmed response inhibiting contingency (DRO) rather than a noncontingent response inhibiting S^Δ. To start the session, the house light was extinguished and the white light (S^{D_1}) was lit. Every twenty-fifth lever press during S^{D_1} was reinforced by delivery of a food pellet; every twenty-fifth lever press also extinguished S^{D_1} and initiated a 10-sec DRO (S^{D_1} off was S^{D_2}). Each lever press during S^{D_2} reset and recycled the DRO (change over delay). At the termination of each S^{D_2}, the S^{D_1} was reinstated. One hundred reinforcements constituted a daily session; water was not available in the operant chamber. Three behavioral indices were recorded: (a) number of responses during S^{D_2}; (b) duration of S^{D_1} presentation; and (c) duration of S^{D_2} presentation.

Experiment 3: FR 15-satiation Schedule

The FR-satiation procedure was basically an FR 15 schedule with the rat's performance determining the total number of food pellets obtained during the session. Again, to begin the session the house light was turned off and the S^D illuminated. During S^D every fifteenth lever press was reinforced by delivery of a food pellet. The session was terminated when the rat failed to receive a reinforcement during a 10-min period (exclusive of the first reinforcement). It was assumed that the rat was satiated at the termination of the session [21]. Water was available ad lib at all times. The following indices were recorded: (a) number of responses; (b) latency to obtain the first reinforcement after onset of S^D; (c) number of reinforcements obtained during the session; and (d) length of time from the first reinforcement to the termination of the session.

Animals

Twenty experimentally naive, male Long-Evans rats, approximately 175 days old at the start of the experiment were used. The rats were housed individually with water available ad lib in the home cages. The rats performed Mondays through Fridays and reached asymptotic performance levels within five weeks.

Six rats were used on the VI schedule and six rats on the DRO-FR procedure. Each rat was maintained at 80% of its pre-experimental body weight. After each daily session and on Saturdays and Sundays, each rat was given food pellets in its home cage to maintain its running weight.

Eight rats were used on the FR-satiation schedule and were divided into two equal-sized groups (two chambers were used in the FR-satiation study). The rats were not maintained at a specified body weight but were deprived of food for approximately 22 hr each day. On Saturdays and Sundays, each rat was given food pellets in its home cage equal to its mean daily consumption during the Monday through Friday sessions.

Drugs

Two relatively low dose levels for each anti-anxiety drug were selected for testing on the basis of the available literature. Chlordiazepoxide HCl (Librium®, Roche) and phenobarbital sodium (Luminal®, Winthrop) were administered as freshly prepared solutions in isotonic saline. Diazepam (Valium®, Roche), oxazepam (Serax®, Wyeth), and meprobamate (Miltown®, Wallace) were administered as freshly prepared suspensions in isotonic saline and Tween 80. In the FR-satiation schedule, d-amphetamine sulfate (Dexedrine®, Smith Kline & French) was also administered as a freshly prepared solution in isotonic saline.

Fifteen minutes before a test session, a rat was injected intraperitoneally (IP) with isotonic saline (9 mg/ml/kg) or with a test drug. Drugs were administered in a random sequence, with at least one week between administrations.

Data Evaluation

Each rat served as its own control. The results of each session served as control values for the next session. The mean and standard error of the mean for control and test values were tabulated. Statistical significance was determined by paired comparison *t*-tests comparing control and test data.

RESULTS

In the VI procedure, the rate and pattern of lever-pressing behavior were typical for a VI 1-min schedule [4]. The effects of administering anti-anxiety drugs or saline on response rates during the VI schedule are illustrated in Fig. 1. Each anti-anxiety agent produced increases in the number of lever presses made by the rats. Only the increase produced by 5.0 mg/kg of oxazepam was not statistically significant.

The effects of anti-anxiety drugs on responding during the DRO-FR schedule are shown in Fig. 2. Both dose levels of chlordiazepoxide, oxazepam, and meprobamate increased responding during DRO. Diazepam at 3 mg/kg and phenobarbital at 20 mg/kg increased responding during DRO, but the lower dose of each drug did not affect responding during DRO. Chlordiazepoxide and phenobarbital increased FR response rates; diazepam, at 3 mg/kg, decreased FR response rates; and meprobamate, oxazepam, and the 1-mg/kg dose of diazepam did not alter FR responding.

The data obtained after administering the anxiolytics, d-amphetamine, or saline on the total number of reinforcements obtained, the latency to first reinforcement, and the rate of responding for the FR-satiation experiment are shown in Fig. 3. Both dose levels of chlordiazepoxide and phenobarbital increased the number of food pellets worked

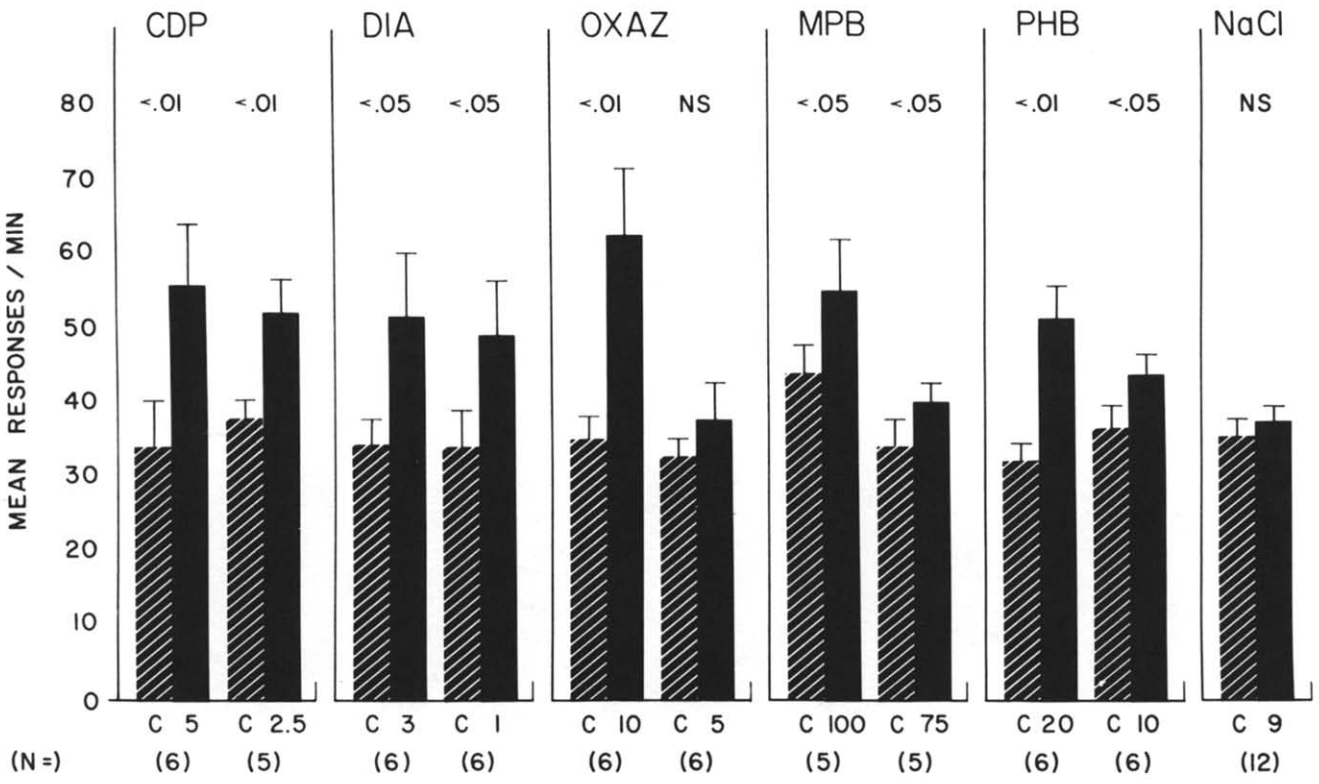

FIG. 1. Effects of chlordiazepoxide (CDP), diazepam (DIA), oxazepam (OXAZ), meprobamate (MPB), phenobarbital (PHB), and isotonic saline (NaCl) on mean responses/min in rats on a VI 1-min schedule. The interrupted bar indicates control (C) rates and the adjacent solid bar shows response rates following drug administration. The number below each solid bar indicates the dose (mg/ml/kg) injected. Vertical ordinates represent the SE of the mean.

for by the rats and decreased the latency to the first reinforcement. Diazepam, at both doses, and oxazepam, at 5 mg/kg, did not affect the acquisition of food pellets. Oxazepam, at 10 mg/kg, decreased the number of food pellets obtained, and diazepam, at 3 mg/kg, increased the latency to the first reinforcement. Meprobamate, at 100 mg/kg, increased the number of food pellets acquired by the rats, but had no effect on latency to the first reinforcement; meprobamate, at 75 mg/kg, had no effect on the parameters measured. d-Amphetamine decreased the number of food pellets worked for and increased the latency to the first reinforcement. None of the anti-anxiety drugs significantly changed the rate of responding in the FR-satiation schedule, but d-amphetamine significantly decreased the rate of responding.

Table 1 summarizes and compares the effects of the anxiolytic agents on the behavior measured in each of the three operant schedules studied.

Disruption of behavior not related to lever-pressing was not observed following administration of any anxiolytic drug. Rats administered d-amphetamine showed a moderate increase in gross motor activity. Administration of saline did not alter any of the indicies recorded.

DISCUSSION

The VI schedule is considered to be a basic operant procedure for demonstrating the effects that drugs have on lever-pressing behavior [17]. According to previous reports [5, 6, 7, 13], higher doses of the anxiolytic drugs tested decreased responding maintained by VI schedules. The doses of the anti-anxiety agents used in the present study uniformly increased responding. Coupled with results from the previous reports cited, the combined data support a dose-dependent explanation for the biphasic increases and decreases in VI responding produced by anxiolytics at low and high doses, respectively.

In previous food-reinforced multiple schedules incorporating S^{Δ} contingencies, the S^{Δ} was considered as a punishment contingency [3], as a noncontingent response inhibiting period [20], or as an extinction contingency [16]. During DRO in the present study, each lever press was punished by delaying the opportunity to respond for food for 10 sec, but responding during DRO was never completely extinguished.

Anti-anxiety drugs have been reported to increase responding during the punishment (and extinction) components of operant schedules [6, 7, 14, 15, 16]. It is possible that the increased responding recorded during the DRO component of the chain schedule, following administration of the anxiolytic drugs, was due to a specific attenuation of the suppressive effects of punishment as Miczek purports [15,16].

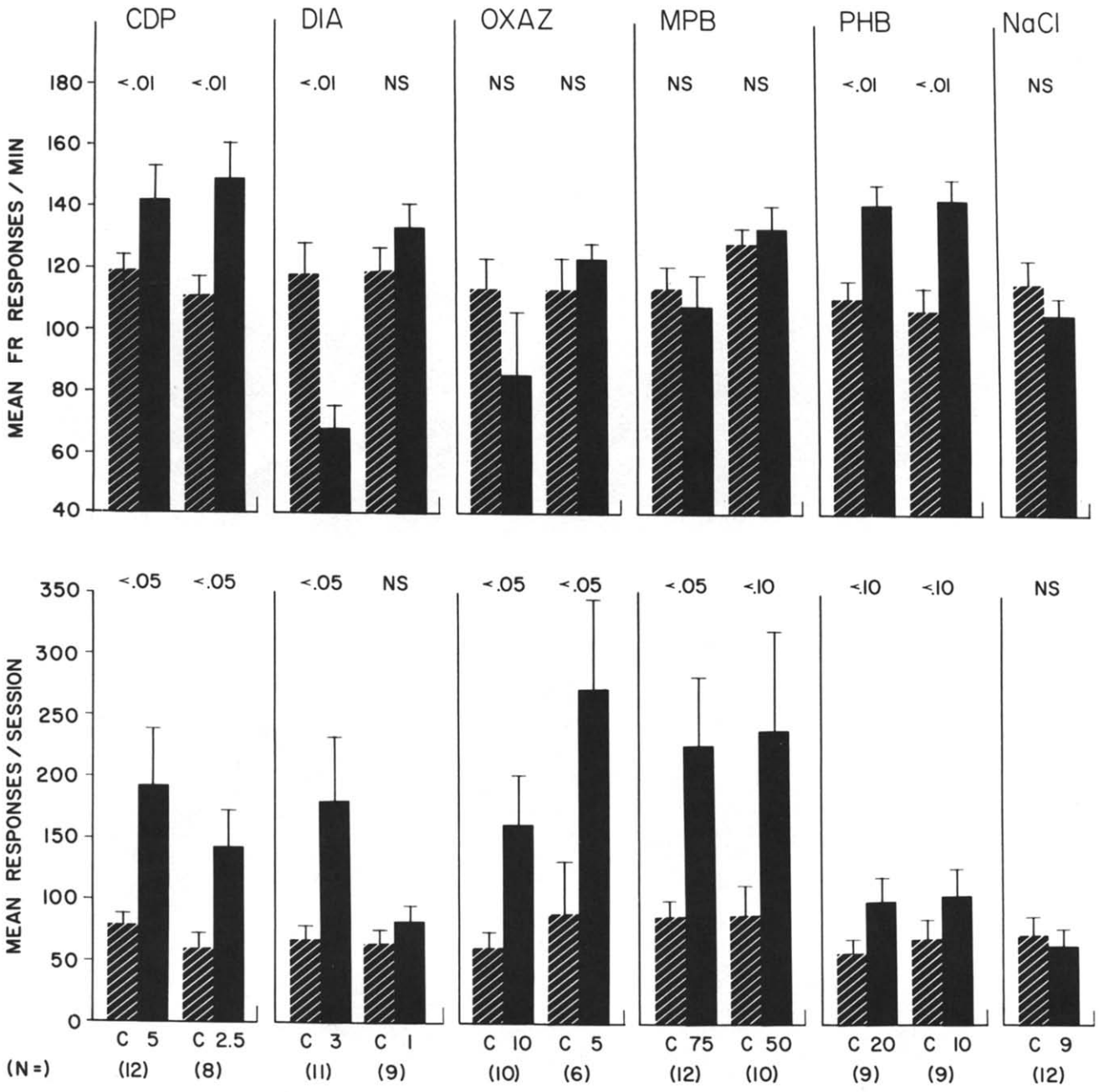

FIG. 2. Effects of anti-anxiety drugs and isotonic saline on mean FR responses/min (top) and on mean responses during DRO/session (bottom) in rats on a DRO-FR schedule. The individual components of the DRO-FR procedure are oriented vertically for each drug. Drug abbreviations and definitions of the figure components are the same as in Fig. 1.

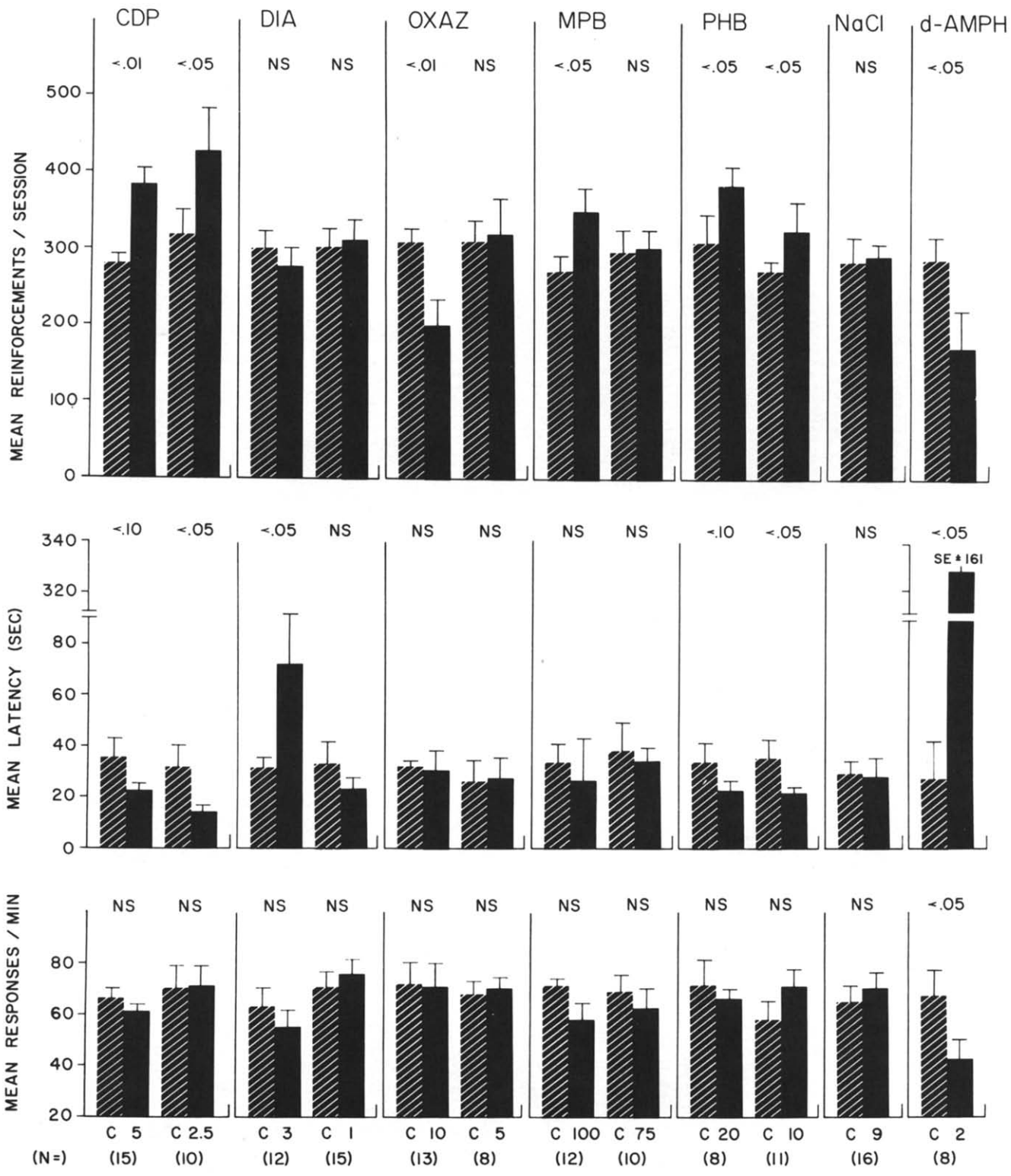

FIG. 3. Effects of anti-anxiety drugs, isotonic saline, and d-amphetamine (d-AMPH) on mean total reinforcements/session (top), mean latency to first reinforcement (sec) (middle), and mean FR responses/min (bottom) in rats on an FR-satiation schedule. The individual components of the FR-satiation procedure are oriented vertically for each drug. Drug abbreviations and definitions of the figure components are the same as in Fig. 1.

TABLE 1

SUMMARY OF THE EFFECTS OF ANXIOLYTIC AGENTS ON VI; DRO-FR; AND FR-SATIATION BEHAVIOR IN RATS

	Experiment 1	Experiment 2		Experiment 3		
	VI Schedule	DRO-FR Schedule		FR-satiation Schedule		
Treatment	Response Rate	FR Response Rate	Responses During DRO	Total Reinforcements	Latency	FR Response Rate
Chlordiazepoxide	↑	↑	↑	↑	↓	NC
Diazepam	↑	↓ or NC	↑ or NC	NC	↑ or NC	NC
Oxazepam	↑ or NC	NC	↑	↓ or NC	NC	NC
Meprobamate	↑	NC	↑ or NC	↑ or NC	NC	NC
Phenobarbital	↑	↑ or NC	↑	↑	↓	NC

↑ = Significant increase over control levels
↓ = Significant decrease below control levels
NC = No significant change from control levels

Alternatively, it should be pointed out that the 10-sec DRO also coincided with the postreinforcement interval (a period of noncontingent inhibition of lever pressing) that typically occurs in FR schedules without S^{Δ} or DRO contingencies. If the rats were not responding due to a noncontingent postreinforcement pause rather than to the operantly conditioned termination of responding during the presentation of S^{D_2}, then it is possible that the increased responding that occurred during the DRO component was the result of an anxiolytic-induced disinhibition of the suppressed lever pressing behavior [14]. However, this alternative appears unlikely since there was stimulus control of the lever pressing behavior as indicated by the relatively low number of lever presses emitted during DRO (Fig. 2) and by the uniform responding patterns recorded on the cumulative record during control sessions.

Although the DRO schedule was selected to study the effects that the anti-anxiety drugs had on a response withholding contingency as compared to an S^{Δ} schedule where lever pressing had no effect on the presentation of reinforcement, the data recorded in the DRO component of Experiment 2 and in the other experiments cited seem to indicate that regardless of how the decrease in lever pressing behavior was maintained, anti-anxiety drugs (dose-dependent) will produce an increase in lever pressing behavior. Wuttke and Kelleher [22] reported a similar observation based on the effects that three benzodiazepines had on punished and unpunished responding behavior in pigeons.

In the FR portion of the DRO-FR schedule, the anxiolytics appeared to produce dissimilar effects on response rates even though previous studies have shown that anti-anxiety compounds generally have a similar activity in a specific behavioral task [10,14]. In a previous FR-S^{Δ} experiment employing a wide range of dose levels [20], chlordiazepoxide produced biphasic effects on the FR response rates during S^{D} presentation. At very low doses, <0.5 mg/kg, IP, there were no changes in response rates; at 0.5–10 mg/kg, chlordiazepoxide produced significant increases in FR response rates, but at 20 mg/kg, response rates decreased significantly to below control rates. Apparently, the dose levels selected for diazepam, oxazepam, and meprobamate coincided with the dose levels that would appear to elicit no effect on or to decrease (as with diazepam at 3 mg/kg) FR response rates in the DRO-FR schedule, even though the same doses increased DRO responding (Table 1). Chlordizaepoxide and phenobarbital produced increases in FR response rates. Obviously, a complete range of dose levels would have to be evaluated to determine if each anxiolytic does, in fact, produce a biphasic effect on FR responding.

The FR-satiation schedule also served to investigate the effects that anti-anxiety drugs had on conditioned FR responding for food and, in addition, evaluated the effects on the motivation for food and the effects on satiation [21]. Chlordiazepoxide and phenobarbital disinhibited or disrupted satiation as indicated by the increase in food pellets acquired and consumed and also appeared to increase the motivation for food as indicated by the decrease in latency to obtain the first reinforcement. Meprobamate, at 100 mg/kg, also disrupted the mechanisms regulating satiation but appeared to have no effect on the motivation for food; the 75-mg/kg dose had no effect on any of the indices recorded indicating that this dose of meprobamate was not affecting the motivation for food or satiation. Diazepam, at 1 mg/kg, and oxazepam, at 5 mg/kg, produced no changes in the parameters measured. Diazepam, at 3 mg/kg, produced a decrease in latency indicating a possible decrease in motivation for food. Oxazepam, at 10 mg/kg, decreased the reinforcements obtained suggesting a facilitation of satiation mechanisms.

In nonoperant, milk-consumption studies, however, all of the benzodiazepine drugs tested in this report increased the amount of milk consumed indicating a disruption or disinhitition of satiation [8,14]. In contrast, in a treadmill-approach experiment with milk reinforcement [8], only chlordiazepoxide at 5 mg/kg (of three benzodiazepine drugs tested) significantly increased the amount of milk worked

for and consumed (or spilled). Diazepam and oxazepam, at dose levels similar to those used in the present study, did not vary the amount of milk worked for in the treadmill-approach task, but at higher dose levels both drugs significantly decreased treadmill activity resulting in a decrease in milk consumption. The results in the FR-satiation schedule and in Gluckman's report [8] suggest that the disinhibition of satiation that is observed in conventional food-consumption tests may not be elicited in an operant schedule and indicate possible differences between the various benzodiazepine drugs. Presently, there is no apparent explanation for the differences observed between the benzodiazepines when tested in the FR-satiation schedule.

Perhaps the most surprising result in the FR-satiation study was the failure for any anxiolytic agent to alter FR response rate, even though in the VI or DRO-FR experiments the same drugs produced significant changes in responding (Table 1). Apparently, the lever pressing behavior in the FR-satiation schedule was so completely controlled by the schedule that the responding behavior was resistant to modification by the doses of the anxiolytic drugs tested [2]; i.e., the rats were conditioned to respond at a constant rate and administering anti-anxiety drugs had no effect on the rate of responding.

d-Amphetamine, however, did modify the responding by rats in the FR-satiation schedule, indicating that responding was susceptible to another class of drugs. The increase in latency to obtain the first reinforcement and the decrease in reinforcements obtained after the administration of d-amphetamine were attributed to the anorexic effects of d-amphetamine [9].

When comparing the FR behavior in Experiments 2 and 3, it is apparent that the procedural differences may have had an effect on the conditioned behavior. For example, the rats in the DRO-FR study were maintained below their normal body weights whereas the rats in the FR-satiation schedule were allowed to maintain their normal body weights. It is known that such differences can produce differences in conditioned responding [4]. Also, the FR response rates in the chain schedule were almost twice as fast as in Experiment 3. This may be the result of the method by which the rates were determined. In the FR-satiation experiment, there were no deductions made for postreinforcement pauses or drinking periods. In the DRO-FR schedule the rate was determined by dividing the number of responses during S^{D_1} in the session (2500) by the duration of S^{D_1} presentation. Since water was not available and the typical postreinforcement interval coincided with the DRO period, the differences in FR rates between the two experiments can be explained.

However, if a comparison is made between the FR response rates in Experiment 2 and the latencies to obtain the first reinforcement in Experiment 3 (instead of comparing FR response rates in Experiments 2 and 3), there is a remarkable similarity between increase, no change, or decrease in response rates in Experiment 2 to a decrease, no change, or increase in latencies in Experiment 3. The similarity is readily apparent in Table 1. This suggests that the changes in the motivation for food produced by the various anti-anxiety drugs tested may have had a direct effect on the FR response rates in the DRO-FR experiment; e.g., the increased motivation for food produced by chlordiazepoxide, indicated by a decrease in latency to obtain the first reinforcement in the FR-satiation schedule, is manifested as an increase in FR response rate in the DRO-FR experiment. Unfortunately, such a discussion cannot explain the fact that the FR response rates in Experiment 3 did not exhibit anxiolytic-induced changes.

Assuming that such a comparison is valid, then some of the apparent interschedule differences produced by the anti-anxiety drugs can be explained, but such a comparison does little to explain the intraschedule differences that may exist between the anxiolytics tested.

At the outset of these experiments, it was thought that all of the anti-anxiety drugs would produce similar effects in each of the operant schedules. The greatest similarities were expected to be in the portions of the schedules that suppressed behavior. Contrary to expectations, as shown in Table 1, there were a number of intra-schedule differences, apparently schedule-dependent, between the anxiolytic agents.

ACKNOWLEDGEMENTS

The author would like to thank Drs. R. G. Babington, B. Beer, D. E. Clody, and M. E. Goldberg for their suggestions and criticism during the preparation of this report. The author is particularly indebted to Drs. P. L. Carlton and D. Frost for critical editing of the manuscript.

REFERENCES

1. Bainbridge, J. G. The effect of psychotropic drugs on food reinforced behaviour and on food consumption. *Psychopharmacologia* (Berl.) **12:** 204–213, 1968.
2. Dews, P. B. Modification by drugs of performance on simple schedules of positive reinforcement. *Ann. N.Y. Acad. Sci.* **65:** 268–281, 1956.
3. Ferster, C. B. Withdrawal of positive reinforcement as punishment. *Science* **126:** 509, 1957.
4. Ferster, C. B. and B. F. Skinner. *Schedules of Reinforcement.* New York: Appleton-Century-Crofts, 1957.
5. Geller, I. Relative potencies of benzodiazepines as measured by their effects on conflict behavior. *Archs int. Pharmacodyn. Ther.* **149:** 243–247, 1964.
6. Geller, I. and J. Seifter. The effects of meprobamate, barbiturates, d-amphetamine and promazine on experimentally induced conflict in the rat. *Psychopharmacologia* (Berl.) **1:** 482–492, 1960.
7. Geller, I. and J. Seifter. The effects of mono-urethans, di-urethans and barbiturates on punishment discrimination. *J. pharmac. exp. Ther.* **136:** 284–288, 1962.
8. Gluckman, M. I. Pharmacology of oxazepam (Serax), a new anti-anxiety agent. *Curr. ther. Res.* **7:** 721–739, 1965.
9. Grossman, S. P. and A. Sclafani. Sympathomimetic amines. In: *Pharmacological and Biophysical Agents and Behavior,* edited by E. Furchtgott. New York: Academic Press, 1971, pp. 269–344.
10. Heise, G. A. Mode of action of anti-anxiety compounds. In: *The Scientific Basis of Drug Therapy in Psychiatry,* edited by J. Marks and C. M. Pare, New York: Pergamon Press, 1965, pp. 165–178.
11. Holister, L. E. Anti-anxiety drugs in clinical practice. In: *The Benzodiazepines,* edited by S. Garattini, E. Mussini, and L. O. Randall. New York: Raven Press, 1973, pp. 367–377.

12. Jarvik, M. E. Drugs used in the treatment of psychiatric disorders. In: *The Pharmacological Basis of Therapeutics,* edited by L. S. Goodman and A. Gilman. New York: Macmillan, 1965, pp. 159–214.
13. Longoni, A., V. Mandelli, and I. Pessotti. Variable interval in rats treated with temazepam, diazepam, oxazepam, and chlordiazepoxide. *Pharmac. Res. Commun.* **3:** 165–173, 1971.
14. Margules, D. L. and L. Stein. Neuroleptics vs. tranquilizers: Evidence from animal behavior studies of mode and site of action. In: *Neuropsychopharmacology,* edited by H. Brill. New York: Medica Foundation, 1967, pp. 108–120.
15. Miczek, K. A. Effects of scopolamine, amphetamine and benzodiazepines on conditioned suppression. *Pharmac. Biochem. Behav.* **1:** 401–411, 1973.
16. Miczek, K. A. Effects of scopolamine, amphetamine, and chlordiazepoxide on punishment. *Psychopharmacologia* (Berl.) **28:** 373–389, 1973.
17. Miller, N. E. Effects of drugs on motivation: The value of using a variety of measures. *Ann. N.Y. Acad. Sci.* **65:** 318–333, 1956.
18. Randall, L. O. and W. Schallek. Pharmacological activity of certain benzodiazepines. In: *Psychopharmacology: A Review of Progress 1957–1967,* edited by D. H. Efron. Washington, D. C.: Public Health Service Pub. No. 1836, pp. 153–184.
19. Richelle, M., B. Xhenseval,. D. Fontaine, and L. Thone. Action of chlordiazepoxide on two types of temporal conditioning in rats. *Int. J. Neuropharmac.* **1:** 381–391, 1962.
20. Wedeking, P. W. Stimulating effects of chlordiazepoxide in rats on a food reinforced FR schedule. *Psychon. Sci.* **12:** 31–32, 1968.
21. Wedeking, P. W. Comparison of chlordiazepoxide and food deprivation in rats on a fixed-ratio satiation schedule. *Physiol. Behav.* **10:** 707–710, 1973.
22. Wuttke, W. and R. T. Kelleher. Effects of some benzodiazepines on punished and unpunished behavior in the pigeon. *J. Pharmac. exp. Ther.* **172:** 397–405, 1970.