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Benzodiazepine Effects Upon Geller-Seifter Conflict Test in Rats: Analysis of Individual Variability

M. BABBINI, M. GAIARDI AND M. BARTOLETTI

Istituto di Farmacologia, Via Irnerio, N° 48, I-40126 Bologna, Italia

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BABBINI, M., M. GAIARDI AND M. BARTOLETTI. *Benzodiazepine effects on Geller-Seifter conflict test in rats: Analysis of individual variability.* PHARMAC. BIOCHEM. BEHAV. 17(1) 43–48, 1982.—The aim of the present study was to investigate in a large group of "drug sophisticated" animals the effect of several doses of oxazepam upon conflict behavior. To this end 43 rats, trained according to the original Geller-Seifter paradigm, were tested with 5 doses (6.25, 12.5, 20.9, 25, and 50 mg/kg IP) of oxazepam. In addition the influence of prior drug experience on the effects of benzodiazepines on punished and unpunished responding was investigated comparing data from the same animals relative to a single oxazepam treatment before and after "drug sophistication." It was found that: (1) after "drug sophistication" oxazepam effect upon the unpunished schedule is decreased, while the disinhibitory action upon punished behavior is increased, unchanged or even decreased; (2) sedative and anticonflict activities of the drug cannot be explained in terms of rate dependency and are independently assessable since, even when unpunished responding is lowered by high doses, the anxiolytic effect is masked in only 27% of the cases; (3) about 20% of the animals appear to be insensitive to the anticonflict effect of oxazepam; (4) the responsiveness to the anxiolytic effect of the drug is related to the shock intensities given during training and to the animal variability under control conditions.

Geller-Seifter conflict test Individual variability Benzodiazepines Learned tolerance Generalization Rate dependency Drug naive animals Drug sophisticated animals

A "MOTIVATIONAL" hypothesis has been used in many instances to explain how aversive stimuli maintain behavior; it has been assumed that aversive stimuli control behavior by generating a generalized state of fear or anxiety, and that drugs can modify this behavior by altering these underlying emotional states. Explanation of drug effects in terms of fear or anxiety reduction have been applied to behavior under the control of punishment, avoidance, and CER paradigms. However drugs often produce differential effects upon behavior under the control of avoidance and punishment schedules. Thus the "motivational" hypothesis, at least in his actual rather simplicist formulation, has appeared to be inadequate.

More recently there has been a growing recognition that the effects of drugs upon aversively motivated behavior depend overwhelmingly on specifiable features of behavior itself and the situation in which it occurs [7,12]. Thus systematic "between tasks" comparisons (e.g., responses contingent vs noncontingent punishment) [9,16] have been performed to evidentiate critical determinants of drug effect; however "within tasks" analyses, which could also provide very useful informations, have been surprisingly scarce, at least as concerns published data. The present experiment was just devised to investigate interindividual variability in response to benzodiazepines; a Geller-Seifter conflict situation [8] was choosen as a test. Margules and Stein [11] observed that the degree and sometimes even the direction of the modification induced in the punishment-depressed behavior by antianxiety drugs could vary depending on whether the animals were given a psychotropic agent for the first time ("drug-naive" animals) or had received such a drug previously ("drug-sophisticated" animals). In our experiment analysis of interindividual variability was undertaken administering several doses of oxazepam to "drug sophisticated" rats. In addition data from the same animals relative to a single benzodiazepine treatment before and after "drug-sophistication" have been compared to speculate about drug-experience as a factor in determining benzodiazepine effect upon punished and unpunished behavior.

METHOD

Subjects

The subjects used were 43 adult male Sprague-Dawley rats (Nos breeding farm) weighing 250–300 g at the beginning of the experiment. They were housed three to a cage with water freely available. Food was available in the home cages until 22 hours before the trial.

The cages were located in a nearby temperature controlled (22±1°C) animal quarter with a 12 hr light-dark cycle (light on: 7 a.m.–7 p.m.).

Apparatus

The test chambers were six conventional operant boxes

supplied with a lever, a dispenser for 70 mg food pellets, a grid floor for foot shocks and a panel for light stimuli presentation. Each box was enclosed in a sound attenuating compartment equipped with a ventilating fan and a 3 W bulb lamp to ensure a low level of lighting during the experimental session. Programming of stimulus events and response contingencies were automated with electromechanical control equipments and printing counters located in an adjoining room.

Drugs

Oxazepam at 6.25, 12.5, 20.9, 25, 50 and 100 mg/kg was suspended in a 5% acacia gum solution containing 1.25% of dimethylsulfoxide and injected IP 30 min before running. During control sessions the animals were treated with the vehicle alone.

Procedure

Five days after arrival in the laboratory the rats were starved for 36 hours. They were then placed in the conditioning boxes and trained to press the lever in order to obtain food on a schedule of continuous reinforcement until they earned the 60th reinforcement. The animals were trained for 10 min on alternate days under the continuous reinforcement schedule after 22 hours of food deprivation. Training was continued for three sessions, by which time the rate of lever pressing was quite stable for all subjects. Rats were then switched to a variable interval (VI) schedule (mean 2 min), with the experimental session being approximately 1 hour in duration. When response rate became relatively stable (on the 7th session) a light above the lever, presented for 3 min periods, signalled a continuous reinforcement schedule and alternated with 12 min dark periods during which the VI schedule was in order. Four of these light-dark periods were presented in a session. After 3 sessions the punishment procedure was introduced during the light periods. Each lever press was still rewarded with food but at the same time punished with a scrambled shock (DC constant current, 0.1 sec of duration) delivered through the grid floor. In order to obtain a sustained but not a complete suppression of punished behavior (which could have masked different degrees of behavioral inhibition under a common zero value, thus hidding differences in drug induced behavioral changes) the intensity of the shock was individually adjusted as follows: starting with 0.05 mA, the intensity was incremented by 0.05 mA if the rat made more than six responses (responses occurring less than 5 sec after the preceeding one were not counted) or decremented by 0.10 mA if the rat did not press the lever during the light period or took more than 5 min to resume lever pressing at the start of the dark period. After 20 trials all animals exhibited a stable behavioral baseline, that is they made very few responses during the punished schedule. The final intensity of shock varied from rat to rat between 0.30 and 0.75 mA (mean 0.45 mA).

Animals were then rendered "drug sophisticated"; to this end they were dosed with various benzodiazepine derivatives on a weekly basis for two months, starting with oxazepam 25 mg/kg (37 rats) or 12.5 mg/kg (6 rats). Finally drug trials were performed treating the animals with the vehicle on Wednesday and with one of the five lower doses of oxazepam on Thursday. For each animal the dose level for a given day was chosen at random from all dose levels remaining to be administered. In addition some rats, whose performance under punished or unpunished schedule was little or unchanged by 50 mg/kg of oxazepam, were treated also with 100 mg/kg dose.

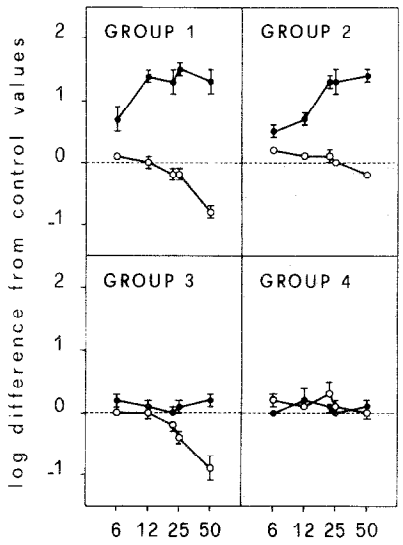

FIG. 1. Dose-response curves of oxazepam for the punished (●) and the unpunished schedule (○). Animals are grouped according to their responsiveness to the drug in the two schedules (see results). Data are expressed as mean differences between the number of lever presses obtained on treatment day and on the preceeding control day (after log transformation).

TABLE 1

FREQUENCY DISTRIBUTION OF THRESHOLDS FOR THE PUNISHED AND THE UNPUNISHED SCHEDULES

Doses (mg/kg)	Percent of rats* Punished schedule	Unpunished schedule
6.2	25.58	0
12.5	32.56	2.33
20.9	16.28	9.30
25.0	2.33	6.98
50.0	2.33	34.88

*Scores refer to the percent of rats for which the dose reported is the lowest effective.

Analysis of Data

As is usual in conflict experiments [1,5] the response of each rat was always expressed as the difference between the logarithms of the total number of lever presses (during the unpunished and the punished schedule) obtained on treatment day and on the preceeding control day. Since the main purpose of the work was to analyze the individual variability of rat's response to oxazepam, a criterion was required to judge the threshold for a pharmacological effect of a given dose in each animal. The differences between successive control trials (which were spaced a week apart), for the unpunished and the punished schedule, were calculated as described above for drug trials thus obtaining for each rat a

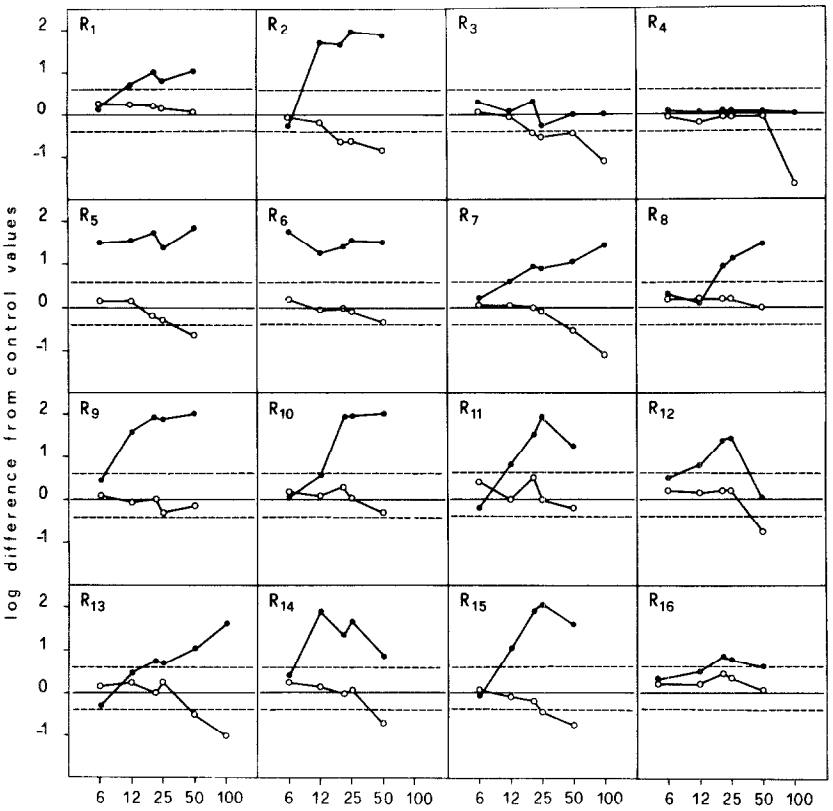

FIG. 2. Dose-response curves of some representative animals for the punished (●) and the unpunished (○) schedule. Data are expressed as differences between the number of lever presses obtained on treatment day and on the preceeding control day (after log transformation). The lines above and below zero represent the highest control-control difference obtained respectively in the punished and unpunished schedule.

sample of 5–6 differences representing the trial to trial variability under control conditions. The criterion was to consider a pharmacological effect only those treatment-control differences exceeding the highest control-control difference obtained (respectively in the punished and the unpunished schedule) in the whole population of 43 animals. Further analyses for the relationship between various training parameters and responsiveness to oxazepam were done by a CHI-square test for linear trend. Data relative to oxazepam effect before and after "drug sophistication" were expressed as already specified and analyzed by the analysis of variance according to a two factor design (groups, period) with repeated measures on one factor (groups).

RESULTS

Using the criterion described under methods, 9 animals (21%) were found to be unresponsive to oxazepam in the punished schedule up to a dose of 50 mg/kg. Three of these were treated also with a 100 mg/kg dose but again there was no change in the behavior under the punished schedule. Regarding the unpunished schedule, 20 rats (46.5%) were found to be unresponsive to oxazepam up to a dose of 50 mg/kg. Four of these rats were treated also with a 100 mg/kg dose which was able to decrease in all animals the number of lever presses. Thus, taking into account the results obtained up to a dose of 50 mg/kg, our rats can be divided into four groups: animals responsive to the drug in both schedules (group 1, n=17), animals responsive only in the punished (group 2, n=17) or unpunished (group 3, n=6) one and animals unresponsive at all (group 4, n=3). Corresponding dose-effect curves are depicted in Fig. 1. Among the rats responsive to oxazepam the lowest dose giving a pharmacological effect varied widely from one animal to another; the frequency distributions of thresholds for the punished and the unpunished schedule are shown in Table 1. The ED_{50}s calculated from these distributions were 15.31 (f.l. 95%: 12.71–18.45) for the punished schedule and 42.03 (f.l. 95%: 37.17–47.52) for the unpunished schedule.

A more detailed picture of the effects of oxazepam during the punished and the unpunished schedule can be achieved from the analysis of the dose-effect curves of each rat. Some representative curves, depicted in Fig. 2, show that for some animals the effect of oxazepam upon the punished schedule was clearly dose-dependent (R_1-R_7-R_8-R_9), while for others the response to the drug seemed of the all-or-none kind (R_2–R_{10}). Moreover, the maximum anticonflict effect was pronounced in some rats (R_2-R_9-R_{10}-R_{11}-R_{15}) but moderate in others (R_1-R_{12}-R_{16}). The relationship between the response in the punished and in the unpunished schedule was also variable. For some rats high doses of oxazepam depressed the behavior in the unpunished schedule and also lessened (R_{14}) or abolished (R_{12}) the anticonflict effect in the punished schedule; for other animals, however, the anticonflict effect

TABLE 2

OXAZEPAM (12.5 OR 25 mg/kg) EFFECT UPON PUNISHED AND UNPUNISHED SCHEDULES BEFORE AND AFTER "DRUG SOPHISTICATION"

Group*	n	Period	Punished schedule†	Unpunished schedule†
1	17	before sophistication	−0.853	0.684
		after sophistication	−0.207	1.505
2	17	before sophistication	−0.537	0.818
		after sophistication	−0.019	1.144
3	6	before sophistication	−0.587	0.743
		after sophistication	−0.268	0.079
4	3	before sophistication	−0.226	0.764
		after sophistication	0.079	0.158

*Animals are grouped according to responsiveness to oxazepam up to a 50 mg/kg dose in the punished and unpunished schedule after "drug sophistication" (see Results).

†Data are expressed as mean differences between the number of lever presses obtained on treatment day and on the preceeding control day (after log transformation). See text for ANOVA.

still increased from 50 to 100 mg/kg (R_7–R_{13}) together with an increase of the depressive effect upon the unpunished schedule. For all the animals tested, however, the lowest effective dose in the punished schedule was generally less than, or at the most equal to, the lowest effective dose in the unpunished schedule.

An important issue in Geller's methodology is to ascertain if, or to what extent, a sedative effect of a given drug could mask its anticonflict activity. It was shown above that this was probably the case for some animals but not for others. As an index of this possible masking effect the difference was taken for each rat between the scores obtained in the punished schedule at 50 and 25 mg/kg doses (this difference should be greater the greater the depressive effect upon the unpunished schedule). A correlation was then calculated between these differences and the scores obtained in the unpunished schedule at a 50 mg/kg dose. The correlation coefficient was r=0.518 which gave a determination coefficient of r^2=0.268.

Since rats exhibited a fairly large individual variability in the pharmacological response to oxazepam some further analysis was done to evaluate possible determinants of this variability. The analysis showed that there was an inverse linear relationship between shock level at the end of training and responsiveness to oxazepam during the punished schedule, χ^2=7.787, $p<0.01$, that is, the higher the shock level the lower the number of rats sensitive to the drug. On the other hand, there was a relationship neither between responsiveness to oxazepam and shock level at the end of the first punished session nor between responsiveness to the drug and time taken to resume lever-pressing after the first shock period. Another analysis was done to investigate the relationship between the trial-to-trial variability under control conditions and response to drug. The standard error of the control-control differences obtained in the punished and unpunished schedule was taken as an index of this variability. It was found that there was a linear relationship, for both the punished, χ^2=4.078, $p<0.05$, and the unpunished, χ^2=3.588; p=0.06, schedule, between the variability of individual baselines and the pharmacological response. Rats having more variable baselines were also more sensitive to drug effects.

Data relative to oxazepam (12.5 or 25 mg/kg) effect upon punished and unpunished behavior, before and after "drug sophistication" (see Table 2), were analyzed by the analysis of variance. It was found that, after "drug sophistication", the depressive effect of oxazepam upon the unpunished schedule was decreased in all groups, F(1,39)=19.17, $p<0.01$, while the disinhibitory action upon punished behavior was increased, group 1: F(1,39)=8.22, $p<0.01$, remained unchanged, group 2: F(1,39)=1.30, p=N.S., or even decreased, group 3: F(1,39)=5.38, $p<0.05$ and group 4: F(1,39)=4.48, $p<0.05$.

Finally data relative to oxazepam effect were analyzed for rate dependency. A regression of the pharmacological effects upon the pre-drug control rates was calculated at each dose for the unpunished schedule in naive as well as in sophisticated animals; for the punished schedule however the analysis was limited to naive rats because the control number of lever presses was 0 or 1 for most of the sophisticated animals. Negative slopes were obtained in naive animals for the unpunished, b=−0.80; t=3.42; $p<0.001$, and the punished schedule, b=−0.63, t=2.09, $p<0.05$. After "drug sophistication" a significant negative slope was obtained only at a 50 mg/kg dose, b=−0.43, t=2.12, $p<0.05$.

DISCUSSION

It has often been suggested from an operational approach that the actions of psychotropic agents are rate dependent. Some investigators [10,17] have attempted to apply a rate-dependency analysis to the effects of benzodiazepines in the conflict paradigm. It was found that these agents exert a specific effect on punished behavior that cannot entirely be explained in terms of rate-dependency. Thus benzodiazepine effects cannot be consistently described as rate dependent, even if, under some circumstances, control rates of responding may have some role in determining behavioral effects of these drugs. Our results give further support to this hypothesis; in fact in naive rats for both the punished and the unpunished schedule the magnitude of the pharmacological effect was related to the pre-drug control rate; however after drug sophistication a similar relationship was evident only for unpunished behavior at a 50 mg/kg dose. It is worth noting that also Cook and Sepinwall [4] report that chlordiazepoxide exert rate dependent effects at a maximally effective dose (20 mg/kg orally) but not at a 2.5 mg/kg dose.

It is generally believed that anxiolytic drugs do not produce their effects upon the conflict-punishment paradigm by removing behavior from the control of a discriminative stimulus [3,14]. Nevertheless Cook and Sepinwall [4] have produced data suggesting that in drug naive rats the initial depression in the unpunished component (VI 30 sec) can be absent in an equivalent schedule with no punishment in the other component (FR 10). Because quite different response rates are generated in both components of a multiple VI 30 sec–FR 10 schedule with, but not without, a punishment contingency, it is tempting to suggest that a weakening of the behavioral control of the discriminative stimulus does exist when animals are given a psychotropic agent for the first time. Some support for this hypothesis is available from our data. In 9 out of 43 rats (animals belonging to groups 3 and 4) a rate increasing effect during the punished schedule was obtained with a 12.5–25 mg/kg dose before drug sophistication; there-

fore doses even 2–4 times greater were unable to produce such an effect, making it highly unlikely that tolerance (by definition a dose related phenomenon) to a true anticonflict action is involved. Moreover, if we consider that, for 8 out of the 9 animals, a depressant action upon the unpunished behavior was obtained after drug sophistication and that for all the responsive animals (group 1 and 2) the lowest effective dose in the punished schedule was generally less than, or at the most equal to, the lowest effective dose in the unpunished schedule, we can conclude that the rate increasing effect observed during the punished schedule in naive animals (groups 3 and 4) was not due to an anticonflict action, but possibly to a generalization phenomenon. On the contrary it appears that generalization from punished to unpunished components does not play a role in determining benzodiazepine effects in drug sophisticated animals, because a dose related decrease in unpunished responding (see data relative to group 1) is obtained together with a steady increase in punished one or a dose related increase in punished behavior (see data relative to group 2) together with a slight increase in unpunished one. Thus we feel that in drug sophisticated (but not in drug naive) animals a decrease in unpunished responding is correlated with the sedative properties of the drug; a similar correlation has been suggested by some also for drug-naive rats [2,11]. It is generally assumed that an increase in punished responding reflects the antianxiety properties of the drug; however, the data presented above indicate that this is probably true only for drug sophisticated animals.

We have observed that, after "drug sophistication," the oxazepam effect upon the unpunished schedule was decreased (tolerance) in all groups, while the anticonflict effect was increased (sensitization) in group 1 and unchanged in group 2. This phenomenon has been already reported by several authors [2, 11, 18] and could depend either on repeated treatment per se or on repeated testing in the treatment state. Sepinwall and Cook [18] have shown that sophistication can take place even if the drug is administered in the home cage after the conflict-punishment paradigm, provided that the drug is given in sufficiently high doses; on the other hand with low doses a "drug sophisticated" profile appeared only when the animals experienced the drug effect during the trial. Therefore it seems that the relative importance of treatment per se and treatment-testing interactions depends on the dose used. Since in our experiment low or moderate doses were administered before the trial, a treatment-testing interaction has probably occurred. It has been suggested that repeated testing in the treatment state can cause a "learned" or "behaviourally augmented" tolerance and that changes in reinforcement density produced by the initial behavioral effect of the drug may be a crucial determinant of whether or not behavioral tolerance will develop [6]. Oxazepam administration to drug naive animals caused a decrease in unpunished responding and thus a reduced frequency of reward. If we consider that the alimentary drive seems to be enhanced by benzodiazepines [15], we can reasonably think that "learned tolerance" aiming to reestablish the pretreatment rate of positive reinforcements played a role in the progressive reduction of the "depressant" component and the progressive enhancement of the "antipunishment" component of oxazepam action. It is worth noting from our data that after drug sophistication the increase of anticonflict effect was statistically significant just in animals (group 1) which still were sensitive to the depressive effect of oxazepam in the unpunished schedule (see Table 2).

As regards interindividual variability in response to benzodiazepines, two major determinants of the responsiveness to the drug seem to emerge from the present study. The first one concerns the variability of rats under control conditions. Animals with more variable baselines appear to be more sensitive to drug effects. Even if it is difficult to explain the cause of this relationship, as external supporting data are lacking, it could be argued that a rat "more variable" means an animal more reactive to different kinds of stimuli and thus also more sensitive to pharmacological stimulation. Another very important factor seems to be the shock level. The responsiveness to the anticonflict effect is inversely related to shock intensities given during training. A similar result has been obtained in the pigeon by McMillan *et al.* [13], who reported that diazepam increased responding suppressed by 4.3 mA considerably more than rates suppressed by 5.2 mA. According to some authors [7,9] benzodiazepines and other agents endowed with anticonflict properties tend to be much more effective when a positively reinforced response is punished by contingent punishment, relative to otherwise similar paradigms employing a classical contingency (CER). However adventitious reinforcement phenomena may lead to learning with contingent shock as if such shock were noncontingent. If we suppose a similar event to be more likely when stronger shocks are employed, we can tentatively explain why shock intensity affects the manner in which drugs alter punished responding. However more recently Rawlins *et al.* [16] carried out a study in which a direct comparison was made between suppression of responding produced by either punishment or conditioned suppression in rats. Shock frequencies were similar in both conditions and shock intensities were varied to ensure that the degree of suppression was also similar under both conditions. The results showed that chlordiazepoxide produced similar attenuations of response suppression produced by both punishment and conditioned suppression. Thus the reason why the responsiveness to the anticonflict effect is inversely related to shock intensities remains to be elucidated; it is worth noting that animals more reactive to the drug are both more sensitive to shock (a lower shock is required to achieve response suppression) and more variable under control conditions.

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