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Acute Administration of Diazepam and Buspirone in Rats Trained on Conflict Schedules Having Different Degrees of Predictability

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COSTELLO, N. L., J. N. CARLSON AND S. D. GLICK. *Acute administration of diazepam and buspirone in rats trained on conflict schedules having different degrees of predictability.* PHARMACOL BIOCHEM BEHAV **40**(4) 787–794, 1991.—The anticonflict activities of diazepam and buspirone were examined on three schedules designed to condition the suppression of licking. The schedules differed in the degree to which they predicted (signalled) the presentation of a conflict inducing electric shock. The first study investigated the effects of three doses of diazepam (0.5, 2, and 5 mg/kg IP) on a predictable, a moderately predictable, and an unpredictable schedule of shock presentation. Diazepam induced a significant increase from baseline in licking during the shock component on all three schedules. These anticonflict effects were the most consistent on the predictable schedule, and least consistent on the unpredictable schedule. A second experiment investigated the anticonflict activity of three doses of buspirone (0.125, 0.25, and 0.625 mg/kg SC) on each of these three schedules. The predictable and moderately predictable schedules failed to detect anticonflict activity at any dose of buspirone. However, the lowest dose (0.125 mg/kg) of buspirone increased shocked licking and the highest dose (0.625 mg/kg) decreased shock component licking on the unpredictable schedule. Thus the unpredictable schedule was sensitive to both anticonflict (anxiolytic) and proconflict (anxiogenic) effects of buspirone.

Anticonflict Predictability Diazepam Buspirone Conditioned suppression of drinking Proconflict

VARIOUS procedures have been used as animal models of human anxiety. Some of these methods are referred to as "conflict procedures" and are based upon the punishment, usually by means of a brief electric shock, of otherwise rewarded behavior. Typically a subject's responding is suppressed when an electric shock is presented, and the conflict induced in the subject is considered to mimic anxiety observed in humans (19,51). These animal models have traditionally been used to screen typical antianxiety compounds such as the benzodiazepines and barbiturates. Recently, it has been suggested that these conflict procedures may have become "tailored" to detecting the anticonflict properties of drugs that act similarly to the benzodiazepines and/or barbiturates (1,15). This idea raises questions about the validity of old methodologies for measuring the anticonflict potential of new or atypical drugs (2).

There has been a resurgence of interest in the role which serotonergic systems play in the mechanisms of anxiety. A major reason for this renewed interest is the recent development of serotonergic drugs that have antianxiety activity (12, 18, 49). One such compound, buspirone, has been shown to be clinically effective and is currently being used as an alternative to the benzodiazepines for the management of anxiety disorders (9, 21, 37, 40, 42) as well as depression (11,43). Buspirone is structurally unrelated to the benzodiazepines and lacks the side effects associated with their use (37,41). The drug is a $5HT_{1A}$ agonist (36) and probably exerts its antianxiety effect through serotonergic mechanisms (8,49). Buspirone's antianxiety profile has been assessed using various animal models including conflict procedures, but the results of such studies have been inconsistent, owing perhaps to differences in the type of conflict procedure, the range of doses, the species of animal used, and the route of drug administration (3, 22, 38). In contrast to clinical findings, conflict models tend to suggest that in comparison to diazepam, buspirone should possess only weak anxiolytic activity.

The anxiolytic activity of buspirone may be dependent upon the predictability of the stress which induces anxiety (1). Buspirone has been observed to be effective in increasing shock-suppressed licking in the conditioned suppression of drinking (CSD) conflict paradigm (31,45). We have developed novel forms of the CSD procedure in which the predictability of the punisher was varied. The effects of diazepam and buspirone were evaluated on three conflict schedules, each with different degrees of stressor predictability.

METHOD

Animals

Subjects were naive female Long-Evans rats (Blue Spruce Farms, Altamont, NY), weighing 225–249 grams at the start of

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the experiment, and were housed three to four per cage and maintained on a 12-h light/dark cycle. Animals had ad lib access to food, and water was restricted throughout each of the experiments.

Behavioral Apparatus

Training and testing were conducted in identical Plexiglas cylinders which measured 30 cm diameter × 30 cm high. Floors consisted of aluminum grid bars spaced 1.75 cm apart. The top of each cylinder was equipped with both a light and a tone. Through one part of the cylinder a metal drinking tube protruded and was connected to a drinkometer, and to a shock source delivered through normally open and normally closed relay contacts respectively. This area of the chamber was lined on the inside with metal so that the Plexiglas could not serve as an insulator from the shock. The shock source was a Lehigh Valley Electronics solid-state shocker. The entire system was housed in a sound-attenuated chamber and was connected to an Apple IIe computer via a Med Associates interface.

Drugs

Diazepam (Sigma Chemical Co.) was prepared as a suspension in 0.5% Tween 80 and 0.9% saline and sonicated. All doses of diazepam were injected intraperitoneally (IP) twenty minutes prior to placement in the testing chamber. Buspirone (Bristol Myers) was dissolved in 0.9% normal saline. Injections of buspirone were made subcutaneously (SC) in the back of the neck fifteen minutes prior to testing. The injection volume was 1.0 ml/kg and the vehicle was normal saline.

Procedure

Training. Initially all rats were placed in the conditioning chambers and allowed free access to a 5% sucrose solution which was used as the reinforcer for both training and experimentation. During training rats were randomly assigned to one of three schedules of shock-induced suppression of licking. Shocks of 0.35 mA lasting 1 s, were delivered according to the particular schedule of shock presentation. Shock was delivered only when the rat made contact with the drinking tube and completed the electrical circuit with the grid floor. The schedules are described as follows:

Predictable Schedule (CSD-like)—This procedure was based upon the conditioned suppression of drinking (CSD) paradigm as previously described (16, 28, 45). A random interval schedule 21 seconds was used in which seven second periods of tone and light were presented. During the first two seconds of tone and light, licks were recorded but not shocked. Shock was delivered for every contact made with the drinking tube during the last five seconds of the tone and light period. This schedule was considered to produce a situation which was highly predictive of conflict periods in that the tone/light combination predicts shock 100% of the time.

Moderately Predictable Schedule (MOD)—This procedure was developed in order to reduce the predictability of the shock presentation. Twenty-four nonshock and twenty-four shock (signalled with tone and light) conflict periods were presented alternately during a ten-minute period. Each of the two five-minute blocks was divided into 12 nonshock (150 s) and 12 shock components (150 s). The length of each individual component was randomly assigned and was either 5, 10, 15, or 20 s in length. All shock components were accompanied by the presentation of a tone and light which remained on throughout the duration of that component. Shocks were presented on a random ratio schedule of four (RR4) so that on average only every fourth lick made by the rat was shocked. This was done in order to make the shock presentation less predictable than that found on the CSD schedule, such that the tone/light combination only occasionally predicts shock.

Unpredictable Schedule (UNP)—This schedule was developed to substantially diminish the predictability of the presentation of shock. The schedule of nonshock and shock presentation was exactly the same as that of the Moderately Predictable (MOD) schedule with the exception that the tone and light no longer signalled the shock component. This was done to diminish the salience of the cues which would allow discrimination between nonshock and shock periods. There is, however, some degree of predictability of the punisher on this schedule, since shock may predict a possible subsequent shock on the punished component.

All rats were trained and tested during ten-minute sessions conducted seven days a week, until stable baselines were obtained consistently for a one- to two-week period. Stability criteria were determined by no significant change in responding which was greater than ten percent from day to day. The licking response acquired during both the shock and nonshock components was equally stable for all three types of schedules from one test day to the next. This produced a reliable testing situation which allowed for comparisons to be made between schedules. To further increase the reliability of these results, rats were matched for baseline responding at each dose level tested. After testing, water was provided in home cages for fifteen minutes so that all rats were equally satiated from day to day (approximately 24 hours of water deprivation).

Experiment 1

For each of four days animals received IP injections of saline vehicle 20 minutes prior to placement in the testing chamber. At the end of the fourth day an average of the number of licks made on the shock and nonshock components on the last three saline days was calculated for each individual animal, and this served as the baseline responding. Subjects that were matched for baseline were assigned to one of three dose groups (0.5, 2, and 5 mg/kg) for administration of diazepam. For the next four consecutive days, animals were injected IP with their respective dose of diazepam 20 minutes prior to the 10-minute testing session.

Experiment 2

For each of 4 consecutive days, animals were injected SC with normal saline vehicle 15 minutes prior to placement in one of three testing chambers. At the completion of the fourth saline day, the baseline for shock and nonshock licks were calculated as stated above. Animals were matched according to baseline and assigned to one of three (0.125, 0.25, 0.625 mg/kg) dose groups for buspirone administration. Testing was conducted for 5 consecutive days upon which rats were injected subcutaneously with buspirone 15 minutes prior to exposure to the testing chamber.

RESULTS

Experiment 1: Diazepam

Conditioned suppression of drinking predictable schedule. Split plot ANOVA on the licks made during the shock components revealed a significant main effect of test day, $F(4,92) =$

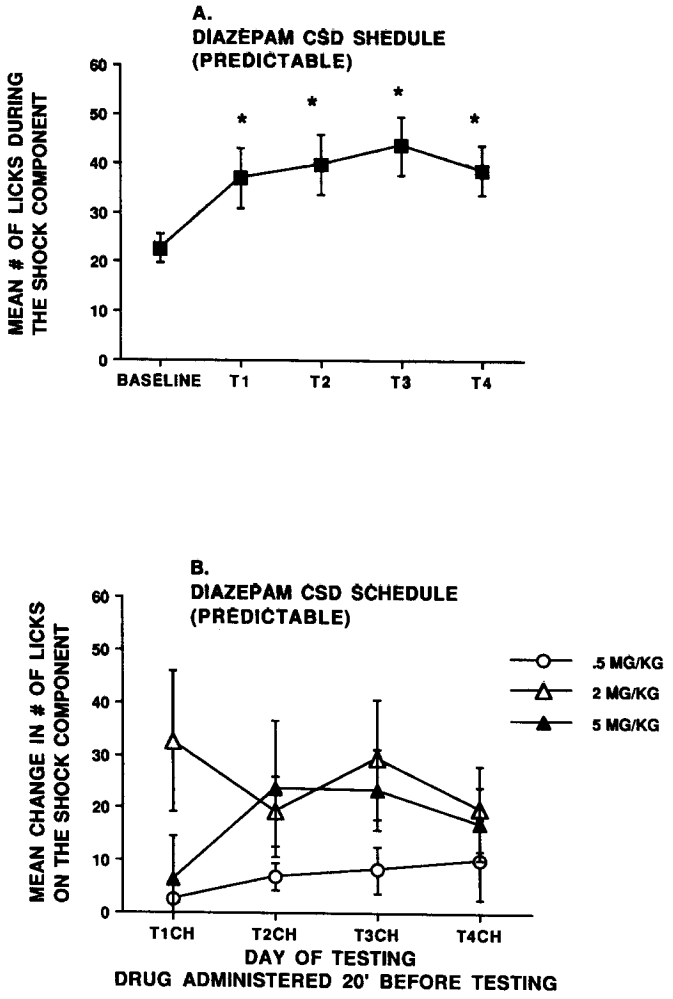


FIG. 1. (A) Data represent the mean (±S.E.M.) number of total licks made during the shock component of the predictable (CSD-like) schedule, over four days of drug testing. Data have been collapsed across three dose groups, 0.5, 2, and 5 mg/kg of diazepam (n=9 for each dose group). Asterisks (*) represent significant increases from baseline $p<0.05$. (B) Mean change from baseline (±S.E.M.) in the number of licks made during the shock component of the CSD-like schedule for each of three doses of diazepam.

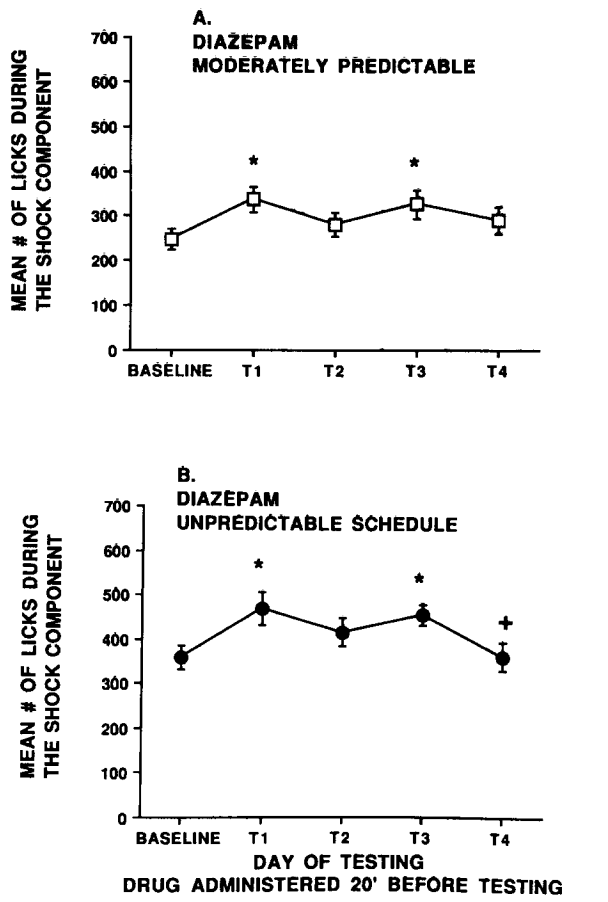


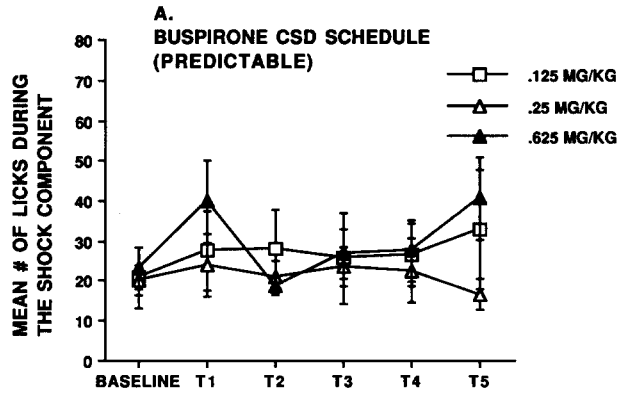
FIG. 2. (A,B) Data represent the mean (±S.E.M.) number of total licks made during the shock component on the MOD and UNP schedules at saline baseline and on each of four drug testing days. Data have been collapsed across three dose groups for diazepam 0.5, 2, and 5 mg/kg (n=9 for each group). Asterisks (*) represent significant increases from saline baseline $p<0.05$. Crosses (+) represent significant differences from days 1 and 3, $p<0.05$.

3.021, $p<0.02$. Repeated measures factorial ANOVA on test day collapsed across dose groups, and post hoc Newman-Keuls multiple comparison tests revealed that relative to saline baseline, diazepam had increased the number of licks made during the shock component on each of the four days of testing, thus inducing an anticonflict effect. Figure 1A represents the mean number of licks made during the shock components of the predictable schedule (CSD) collapsed across dose.

Figure 1B represents the mean change from saline baseline (difference scores) in the number of licks made on the shock component. Split plot ANOVA with Dose and Test as variables revealed a significant main effect of dose group, $F(2,23)=4.292$, $p<0.02$. The lack of an interaction indicated that the changes in shocked licking produced by various doses of diazepam across testing were not significantly different from one another. Repeated measures ANOVA on overall change from baseline collapsed across test revealed a main effect of dose group, $F(2,23)=3.704$, $p<0.05$. Diazepam induced a dose-dependent change in the number of licks made during the shock component (punished responding) with the doses of 2 and 5 mg/kg producing the greatest effects.

The sucrose solution is consumed primarily during the nonshock component of this schedule, and is an appropriate measure of unpunished responding. Split plot ANOVA and post hoc comparisons of sucrose consumption data (unpunished responding) for the baseline plus the four days of drug testing revealed that only the 5 mg/kg dose significantly altered the amount of solution consumed from baseline. This dose significantly decreased sucrose consumption, but only on the fourth test day.

Moderately predictable schedule. The results of a split plot ANOVA on the number of shock licks on the MOD schedule, showed that diazepam significantly increased the number of licks on the shock components of the test days, $F(4,96)=4.689$, $p<0.002$. This effect was nondose dependent. Data were collapsed across dose, and repeated measures ANOVA with post hoc Newman-Keuls multiple comparisons were performed. Results indicated that the first and third days of drug administration were significantly greater than the baseline days in the number of licks made on the shock components (Fig. 2A). Sim-



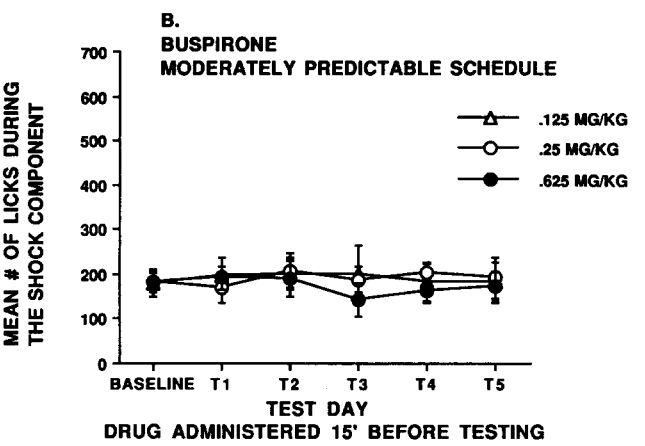
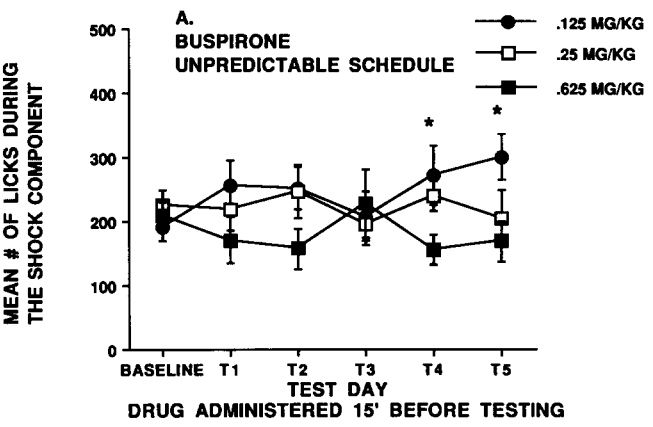


FIG. 3. (A,B) The effects of three doses of buspirone upon (0.125, 0.25, 0.625 mg/kg SC) schedules with tone and light as conditioned stimuli (predictability stimuli) are illustrated. Mean (±S.E.M.) number of total shock component licks on the CSD-like (n=8 to 10) and MOD schedules (n=9) over five consecutive days of testing with the drug.



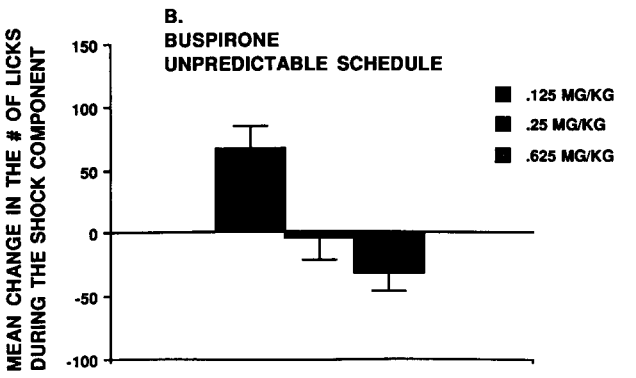


FIG. 4. (A) Data represent the mean (±S.E.M.) number of licks made during the shock component at baseline and after administration of three doses of buspirone (0.125, 0.25, 0.625) on five consecutive days of drug testing. Asterisks (*) represent significant differences from saline baseline, $p<0.05$. (B) Overall mean change from saline baseline (±S.E.M.) in the number of shock component licks. Change data have been collapsed across 5 days of testing. One-way ANOVA: Dose, $F(2,24)=9.108$, $p<0.001$.

ilar analyses of licks during the nonshock component revealed that the drug had no effect on licking.

Split plot ANOVA results from data on the mean change from baseline produced on each day, revealed a significant main effect of test day, $F(3,72)=2.6$, $p<0.05$. Unlike the predictable schedule, all doses of the drug were equally effective on this schedule.

Results of split plot ANOVA on 5% sucrose consumption, for baseline and four days of testing with diazepam revealed that there was a main effect of dose group, $F(2,23)=9.00$, $p<0.001$, but no effect of test day and no interaction. Further analysis revealed that on days 3 and 4 of testing, the consumption for the 2 mg/kg group was greater than that of the other two dose groups. Split plot ANOVA on change in intake (drug-vehicle baseline) showed that there were no significant differences in the change in consumption from baseline over the four days of testing; dose group, $F(2,23)=1.4$, and test day, $F(3,69)=1.63$, ns. Sucrose consumption is a good measure of unpunished responding on the predictable schedule (CSD-like), but may not be an appropriate measure on the MOD or UNP schedules, since they generate large amounts of shock and nonshock licking, and as such may not truly reflect licking exclusively observed on the unpunished part of the schedule.

These results suggest that the MOD schedule is an accurate predictor of the anticonflict potential of diazepam and may be more sensitive for the detection of such effects at lower doses of the drug. However, these acute effects are not as stable as those observed on the CSD-like schedule since they were only observed on two of the four days of testing.

Unpredictable schedule. The mean number of licks made during the shock component of the UNP schedule are depicted in Fig. 2B. There was a significant effect of test day, $F(4,96)=5.729$, $p<0.001$, but no effect of drug dose as determined by a split plot ANOVA. Repeated measures ANOVA on overall shocked licking, collapsed across dose revealed a main effect of test day, $F(4,104)=5.531$, $p<0.001$. Newman-Keuls multiple comparisons test showed that diazepam significantly increased

the number of licks made on the shock component on the first and third days of testing. The fourth test day was significantly lower than the first and third days ($p<0.05$) and no different from baseline (Fig. 2B). Similar significant increases in licking on the first and third day of drug testing were observed during the nonshock component of the schedule. This of course is not surprising since the two components are very similar to one another on the unpredictable schedule.

Analyses performed on change from baseline revealed a main effect of test day, $F(3,78)=4.38$, $p<0.05$, and post hoc Newman-Keuls multiple comparisons showed that the change produced on the last day of testing was significantly lower than that of the first and third days of testing ($p<0.05$). The overall results indicate that diazepam effectively increases shocked licking on the UNP as well as on the MOD and highly predictable CSD schedules.

Experiment 2: Buspirone

Conditioned suppression of drinking predictable schedule. Figure 3A depicts the mean number of licks made during the shock component of the predictable (CSD) schedule. Split plot ANOVA of licking, sucrose consumption and change from baseline measures revealed no significant main effects. This indicates that buspirone, at the doses tested, does not exhibit anticonflict potential on this schedule.

Moderately predictable schedule. Figure 3B illustrates the mean number of licks measured on the shock components for each of the five days of drug testing on the moderately predictable (MOD) schedule. Split plot ANOVA on licking data revealed that buspirone lacked anticonflict activity on this schedule. Consumption decreased slightly by the fourth day of testing in the 0.625 mg/kg dose group.

Unpredictable schedule. The overall results obtained with the UNP schedule are illustrated in Fig. 4A and B. Results of split plot ANOVA indicated that there was a significant interaction of dose group with test day, $F(10,120)=2.037$, $p<0.05$. Post hoc comparisons revealed that the lowest dose of buspirone (0.125 mg/kg) induced a significant increase in the number of licks made on the shock component by the fourth and fifth test day, thus indicating an anticonflict effect for this dose. Similar analyses conducted on nonshock component licks revealed no significant main effects and no interaction, indicating that the drug differentially influenced the two components of this schedule. This is in contrast to the findings with diazepam which induced increases in licking on both components of this schedule. This substantiates the validity of this schedule as a conflict procedure.

To determine if there was a dose effect on shocked licking from baseline to drug testing (saline vs. drug), data from drug test day were collapsed over the five drug test days and reanalyzed using a repeated measures ANOVA; there was a significant interaction of dose group with test day, $F(2,24)=9.108$, $p<0.001$, indicating that the administration of the 0.125 mg/kg dose of buspirone resulted in an anticonflict effect, while the 0.625 mg/kg dose induced a proconflict effect.

The overall change (drug test-baseline; Fig. 4B) produced in shock component licks was also analyzed by a split plot ANOVA. A significant main effect of dose group, $F(2,24)=9.1$, $p<0.001$, was observed. The 0.25 mg/kg dose was without effect. Analysis of sucrose consumption data revealed that the 0.625 mg/kg dose of buspirone significantly decreased the amount consumed but only on the last day of testing. This is not surprising if one considers that both nonshock and shock components contribute to the consumption observed and that the drug is exerting proconflict effects at this dose (i.e., animals are avoiding the spout).

DISCUSSION

Human anxiety can be characterized by a vast number of symptoms which are manifested in disorders such as phobic anxiety, panic attacks, and anxiety mixed with depression (7,17). This makes anxiety difficult to define and study using animal models (2). Traditional screening procedures have failed to yield consistent results in the detection of the anxiolytic activity of novel compounds such as buspirone. It has been conjectured that these traditional models have become "tailored" to be most sensitive to the benzodiazepine class of anxiolytics (1, 2, 4, 27). Furthermore, it has been proposed that drugs which possess properties similar to buspirone may be more effective with anxiety associated with unpredictable stress, typically associated with depression (1, 42, 43). This idea is supported by a number of clinical observations which indicate that buspirone and its analogues are also effective antidepressants (9, 10, 42).

The present set of experiments used three conflict techniques to evaluate the ability of punisher predictability to affect the sensitivity of the conflict methodology to the antianxiety profiles of both diazepam and buspirone. Previous studies have shown that diazepam effectively increased the number of licks made on the shock component in the conditioned suppression of drinking (CSD) conflict procedure (28,31). In the present study, diazepam increased the number of shock component licks on the CSD-like schedule (predictable) with the 2 and 5 mg/kg doses inducing the greatest degree of change. On the moderately predictable schedule (MOD), diazepam also increased punished responding. Unlike the predictable schedule, all doses of diazepam were equally effective in producing a significant change from baseline. This suggests that this schedule may be more sensitive to the anticonflict activity of lower doses of drugs in the benzodiazepine class. However, there were no significant increases or changes in shocked licking observed on two of the four test days. This raises questions about the stability or "consistency" of the anticonflict effect observed with this type of schedule. The data indicate that although shock presentation is less predictable than that of the CSD-like schedule, diazepam still exhibits its anticonflict activity even at lower doses. Presumably, this suggests that while decreasing shock predictability increases the sensitivity to acute diazepam administration, it also decreases the stability of the response observed from one test day to the next.

Since the unpredictable (UNP) schedule contains fewer conditioned stimuli which predict shock presentation, it might be expected that diazepam's ability to attenuate an animal's reactivity to significant stimuli would be quite different from that observed with the other two schedules. Once again, diazepam was effective in increasing punished responding. Comparable to the MOD schedule, this effect was only observed on two of the four test days (days 1 and 3). The number of licks made on the shock component on day 2 was not significantly lower than those on days 1 and 3, thus suggesting that the effect had not been completely abolished on this day. However, on the fourth day of testing, there was a decrease in shock licking observed which was significantly lower than the licking seen on days 1 and 3. This may be interpreted as reflecting a tolerance to the anticonflict effects of diazepam. This suggests once again that decreasing punisher predictability also decreases the stability or "consistency" of the anticonflict effect from one test day to the next. The UNP schedule may be more sensitive to other drug

effects not typically observed in traditional conflict models since some tolerance was observed on day 4 of testing. Baseline levels of responding on both shock and nonshock components are stable from day to day. The lack of anticonflict activity on days 2 and 4 is not due to a "ceiling effect" since diazepam does reliably increase punished responding on alternate test days. One explanation for this phenomenon may lie in the fact that we used female rats as our subjects. Recent studies using another animal model of anxiety have found that diazepam, unlike buspirone, loses some of its anxiolytic efficacy depending upon the time the drug is administered during the estrus cycle (14). However, if this were the only explanation, we would have expected to observe similar diminished efficacy in the rats tested using the predictable schedule.

Buspirone has been found to have anxiolytic activity in some animal models of anxiety, but is either ineffective (4) or anxiogenic in others (35, 48, 53). The data in conflict models are especially complicated, and it has been proposed that the effects of buspirone and similar drugs acting on the serotonergic system, may be dependent upon the particular testing situation (6, 18, 48). Subcutaneously administered buspirone did not induce significant increases in punished responding either on the predictable CSD-like or MOD conflict schedules at any of the doses tested. Perhaps the doses used were too low since other conflict procedures have used higher doses of buspirone and have observed significant effects (38). However, the present results contrast with those of another study which used similar doses of buspirone and observed significant changes in punished licking (31). This study collected data over the course of several weeks during which one drug test session was conducted per week, while the present investigations used consecutive drug exposure testing days, different shock parameters, and a longer duration of training. In addition, the present study used different statistical procedures. The CSD-like and MOD schedules used here are clearly inadequate to test for the anticonflict activity of buspirone. The unpredictable schedule did detect the anticonflict activity of a low dose of buspirone (0.125 mg/kg) and thus was much more sensitive to its activity than either of the other two schedules. When the data were evaluated for change in licking on the shock component with test days collapsed, the highest dose of buspirone (0.625 mg/kg) resulted in a decrease in the number of licks observed during the shock component. A decrease in the number of licks on the shock may be considered to be anxiogenic or proconflict effect. It is interesting that this anxiolytic effect was not observed until the last two days of repeated drug testing. This finding correlates with the clinical and experimental evidence that the drug must be given chronically in order to observe anxiolytic effects (20, 26, 45).

There is further experimental evidence that buspirone decreases punished responding. One study observed a decrease in punished licks, as indicated by a negative difference score, yet concluded that the drug was inactive (3). Recently, high doses of buspirone were observed to suppress the punished responding of squirrel monkeys, thus indicating a proconflict effect (53). Increasing doses of buspirone have been observed to have a dual effect upon performance in a Vogel conflict task (52). The latter study showed that low doses of buspirone induced an anticonflict effect, while higher doses resulted in a reduction of the number of animals approaching the drinking spout. As was observed in the present study, there was no evidence of ataxia or sedation. Furthermore, the present findings reveal that a high dose of the drug (0.625 mg/kg) did not affect either the punished (shock component) or the nonshock components (unpunished) in the parallel schedule designed to be moderately unpredictable, but still induced a proconflict effect on the UNP schedule. If this effect were due to sedation or ataxia, it would be expected that the drug would produce this effect equally on each of the schedules. In addition, buspirone and some pharmacological analogues, 8-OH-DPAT, gepirone, and ipsapirone, have been found to have anxiogenic activity in other animal models of anxiety such as the elevated plus maze and the Montgomery conflict test (25, 35, 48). Similar to our findings, the latter studies observed biphasic effects of low and high doses of buspirone. The fact that buspirone and its analogues exhibit some anxiogenic activity may not be surprising since clinical studies indicate that some patients experience dysphoria and other unpleasant effects such as increased anxiety and mania when using this drug (5, 29, 32).

It should be noted that although buspirone is a $5HT_{1A}$ agonist, it also exhibits moderate affinity for other 5-HT binding sites (36). Furthermore, there is evidence that buspirone also exhibits antagonist activity at $5HT_{1A}$ receptors (39,47). These receptors are found in highest density in the hippocampus, raphe, and cortex (34), the brain regions which are thought to be involved in the control of anxiety states, i.e., the septo-hippocampal system (23). The results of lesion studies indicate that $5HT_{1A}$ receptors may be located presynaptically on the cell bodies in the dorsal raphe (50) and postsynaptically in the hippocampus (24). There is evidence to suggest that these drugs both mimic and decrease the effects of 5HT (46), and that these effects may be the result of activity at $5HT_{1A}$ receptors in the hippocampus and dorsal raphe respectively. However, some studies suggest that buspirone is a partial agonist at these hippocampal receptors (33,44). Perhaps the present findings reflect differential effects of buspirone in these brain regions and/or agonist/antagonist activity at this receptor site. In addition, they may reflect effects attributable to changes in receptor sensitivity which may occur as a result of exposure to chronic conflict during the training period.

The dose of buspirone and the predictability of the punisher appear to have interacted to produce the biphasic effects observed in this study. The present findings lend considerable support to the idea that both diazepam and buspirone may have different effects when tested in different models of anxiety. They further suggest that these differences are related to the interaction between the stressor predictability typically inherent in the model and the activity of different doses of the drug. Different doses of buspirone may have distinctive effects on different subpopulations of serotonergic receptors, and exposure to different types of predictable stress may differentially influence the activity of serotonin utilizing transmitter systems. This might account for the bidirectional effects of this drug in the present study.

ACKNOWLEDGEMENT

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