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Effects of Buspirone in the Geller-Seifter Conflict Test With Incremental Shock

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ABSTRACT

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The novel anxiolytic buspirone has weak or inconsistent activity in most of the animal models commonly used to identify anxiolytics. Among the six published studies of the effects of buspirone on punished level-pressing in the rat, only one reported a clear effect (at two doses), and the peak effect was half that of diazepam. In the present study, in which rats responded for food in a Geller-Seifter conflict procedure with incremental shock, five factors were examined for influence on the effects of buspirone upon punished lever-pressing: 1) fixed-ratio 10 vs. fixed-ratio 1 in the punishment portion of the multiple schedule, 2) drug-naive vs. drug-experienced rats, 3) albino vs. hooded rats, 4) SC vs. PO injection, and 5) time course up to 2 hr. The benzodiazepine chlordiazepoxide robustly increased responding punished by foot-shock, but under none of the conditions did buspirone produce more than a small, inconsistent increase. Punished level-pressing in the rat appears not to be an adequate method for identifying buspirone-like anxiolytics.

Key words: anxiety, anxiolytic, chlordiazepoxide, punishment, response-contingent shock, animal model, rat

INTRODUCTION

Buspirone is a recently approved anxiolytic that differs structurally and pharmacologically from benzodiazepines, propanediol carbamates, barbiturates, and other compounds used for anxiolysis [Goa and Ward, 1986; Eison and Temple, 1986; Lader, 1988]. It does not bind to the benzodiazepine receptor or enhance the action of GABA [Riblet et al., 1982; Eison and Temple, 1986]. Its therapeutic effect occurs with chronic but not acute administration [Goa and Ward, 1986].

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Buspirone is active in some animal models of anxiety but not in others (Table 1). Although all of these models register positive effects of benzodiazepines and other conventional anxiolytics, the first six models listed have been examined in few laboratories and are not widely used to screen potential anxiolytic compounds; the drug-class specificity of each can be questioned. The effects of buspirone in these six models are noted here for comparison with effects in other models.

Buspirone's capacity to increase responding suppressed by punishment in the pigeon is robust, although it has been demonstrated by only one group of researchers. The effect on punished responding in the monkey is weak or inconsistent.

Buspirone's effect on punished drinking in the rat [Vogel et al., 1971], which appears to be the most widely used screening method, is likewise weak or inconsistent. In some of the reports of strong positive results, procedural detail is scant. We have been unable to replicate the strong effect. Although we have manipulated several variables—e.g., strain of rat, light/dark cycle, route of injection, pretreatment time—typically we find one dose active in a dose-effect determination under a given set of conditions, whereas chlordiazepoxide, by comparison, is always active at several doses (unpublished observations).

Of the published studies in which the effects of buspirone on punished level-pressing in the rat were examined, one showed clear effects at two high doses (peak effect was half that of diazepam) [Young et al., 1987], one showed a weak effect at a single dose [Sullivan et al., 1983, an abstract], one contained inadequate data [Geller and Hartmann, 1982], and three showed no effect. Conventional anxiolytics increase responding suppressed by punishment under the procedures used in these studies. The data indicate that the effects of acute buspirone differ from the effects of conventional anxiolytics in punished level-pressing in the rat.

Our own previous data on the effects of buspirone in a modified Geller-Seifter test with incremental shock were inconclusive. Various doses between 2.5 and 20 mg/kg injected PO at 0, 30, 60, or 120 min before the 1-hr session revealed some trends toward an anti-punishment effect: e.g., with 60-min pretreatment, increases of 13% at 5 mg/kg, 28% at 7.5 mg/kg, and 40% at 10 mg/kg. However, the only significant changes were decreases in unpunished responding at doses of 5 mg/kg or greater.

The objective of the present study was to manipulate several variables in an attempt to find a set of conditions under which buspirone would produce a robust increase in punished lever-pressing in the rat. The basic tool was the Geller-Seifter conflict test [Geller and Seifter, 1960] with incremental shock [Pollard and Howard, 1979]. In this procedure, rats press a lever for food in daily 1-hr sessions on a multiple variable-interval 2-min fixed-ratio 1 schedule with responses in the fixed-ratio portion punished by foot-shock—mult VI 2-min (food) FR 1 (food + shock). In Experiment 1, FR 10 (food + shock) was compared to FR 1 (food + shock) in separate groups; FR 10 showed no advantage. In Experiment 2, drug-naive rats were used; they showed no advantage over the drug-experienced rats of Experiment 1. In Experiment 3, albino rats were used; they showed no advantage over the hooded rats of Experiment 1. In Experiment 4, injections were given SC instead of PO; this route showed no advantage. In Experiment 5, injections were given 15 min before the first punishment period, and the effects were measured every 15 min during a 2-hr session; this time-course analysis revealed no consistent anti-punishment effect of buspirone. We concluded that anti-punishment effects of buspirone in the rat are indeed weak and inconsistent and that this procedure is inadequate for identifying buspirone-like anxiolytics.

GENERAL METHOD

Subjects

Ovariectomized Long-Evans rats were used in Experiments 1, 2, and 5, ovariectomized CD albino rats in Experiments 3 and 4. All came from Charles River Laboratories, Wilming-

TABLE 1. Effects of Buspirone in Several Animal Models of Anxiety

Doses tested (mg/kg)	Route	Pre-treat time (min)	Doses having positive effect	Reference
Two-compartment (rat)				
0.1, 0.6, 1,2, 2.5	SC	15	0.1 (weak)	Pich & Samanin [1986]
Elevated plus-maze (rat)				
0.5, 1, 2, 4, 8	IP	30	None	Pellow et al. [1987]
			None	Moser [in press]
0.025–5			None	Critchley & Handley [1988]
0.5, 20	IP	30	None	Pellow & File [1986] (see Pellow et al. [1985], Pellow [1986])
Social interaction (rat)				
	IP		0.25, 0.5 (dim light)	File [1984]
5, 10, 20	PO	30	↓ at 5, ↑ at 10, 20	Guy & Gardner [1985]
Into dorsal raphé		5	40 ng, 200 ng	Higgins et al. [1987]
Face to face (social interaction) (mouse)				
3, 10, 30	SC	30	10	Schreur [1988, abstr.]
Potentiated startle (rat)				
0.6, 1.25, 2.5, 5	SC		1.25, 2.5, 5	Kehne et al. [1988] (see Davis [1986], Davis et al. [1988])
Shock probe (rat)				
0.63–40	SC	60	None	Meert & Colpaert [1986]
Punished lever-pressing (monkey)				
0.5, 1, 3	IP, IM		0.5, 1, 3 (inadequate)	Geller & Hartmann [1982]
1.25, 2.5, 5			None	Sullivan et al. [1983, abstr.]
To 50			None	M.E. Goldberg et al. [1983]
3, 10, 30	PO	30	3, 10 (weak)	Weissman et al. [1984]
0.01, 0.03, 0.1, 0.3	IV	10	None	Wettstein [1988]
Punished key-pecking (pigeon)				
0.01, 0.03, 0.1, 0.3, 1, 3, 10	IM	5	0.03–3	Barrett et al. [1986]
0.03, 0.1, 0.3, 1, 3, 10	IM	0	0.03–3	Witkin & Barrett [1986]
0.1, 0.3, 1, 3, 5.6	IM	5	0.1–5.6	Witkin et al. [1987]
0.1, 0.3, 1, 3, 10	IM	0	0.1–10	Mansbach et al. [1988]
Punished lever-pressing (rat)				
2.5, 5	IP	30	2.5, 5 (inadequate)	Geller & Hartmann [1982]
1.25–40			10 (weak)	Sullivan et al. [1983, abstr.]
1, 3, 10	IP	15, 30	None	Amrick & Bennett [1986, abstr.]
0.5, 1, 2, 5, 10	IP	30	None	Gardner [1986]
0.3, 1, 3	IP	60	None	Mason et al. [1987]
5, 10, 20, 30, 40	PO	30	20, 30	Young et al. [1987]
Punished drinking (rat)				
10, 20, 40, 80	PO		20, 40, 80	Oakley & Jones [1983]
1.25–20			None	Sullivan et al. [1983, abstr.]
0.5, 1, 2, 5	PO	10	1, 2 (weak)	Weissman et al. [1984]
30, 90	PO	30	90	File [1985]
1, 3, 10	IP	30	None	Sanger et al. [1985]
0.5, 1, 5, 8, 10	PO		1, 5, 8, 10	Taylor et al. [1985]
2, 5, 10	PO		None	Budhram et al. [1986]
10	PO	15	10	Eison et al. [1986]
2, 5, 10	PO		None	Gardner [1986]
0.1, 0.6, 1.2, 2.5	SC	15	0.6, 1.2 (weak)	Pich & Samanin [1986]
0.32, 1, 3.2, 5.6, 10	IP		5.6, 10	Heym et al. [1987, abstr.]
0.25, 0.5, 1, 2, 4	IP	10	1, 2, 4 (weak)	McCloskey et al. [1987]
1.25, 2.5, 5, 10	IP	30	5, 10	Shimizu et al. [1987]
10, 20, 40	PO	30	20	Shimizu et al. [1987]

ton, MA. They were housed four per cage in animal quarters on a reverse light/dark cycle (lights on 1600–0400) with water freely available.

Apparatus

Training and testing were done in Coulbourn operant chambers inside Coulbourn enclosures. Each chamber was equipped with a pellet dispenser (45-mg BioServ pellets), a water bottle, a grid floor, and an intelligence panel. The panel had a house light at the upper center, a feeder bin at the lower center, a lever manipulandum at the lower left, and a set of three jewel lights just above the lever. The three lights were linked to operate as a unit, either on or off, and will be referred to as the cue light.

Coulbourn shockers delivered 60-Hz 500-msec pulses to the grid floor through a custom-made current intensity stepper. Control and data acquisition were done by a Data General NOVA 3/12 minicomputer via an InterAct interface.

Procedure

Initially subjects were deprived of food for 24 hr and allowed to acquire the lever-press response in several 15-hr nightly sessions on a progressive ratio schedule in which the number of lever presses required for each pellet delivery increased stepwise from one to 31. When subjects reliably pressed the lever at the highest ratio, they were switched to daily 1-hr sessions (generally 6 days per week, Sunday–Friday) on the final schedule without shock. From this point on, food was available in a feeding cage for 1 hr post-session or in the home cage for 2 hr on days when the subjects were not run. The schedule was similar to that used by Geller and Seifter [1960] as modified by Pollard and Howard [1979]. The multiple schedule consisted of four periods of variable-interval reinforcement, in which a pellet was delivered for a lever-press every 2 min on the average, and four interspersed 3-min periods of fixed-ratio 1 reinforcement signaled by the cue light, in which a pellet was delivered for each lever-press [mult VI 2-min (food) FR 1 (food)] or, for one group in Experiment 1, each tenth lever press [mult VI 2-min (food) FR 10 (food)]. After several sessions on this schedule, shock was introduced in the signaled FR periods so that each pellet was accompanied by a foot-shock that began at 0.00 mA and increased by 0.05 mA with each additional pellet; the shock intensity was reset to 0.00 mA at the beginning of each of the four FR periods in a session. The FR periods, in which both food and shock were delivered, will be called "conflict" periods. Generally we will use the term "responses in conflict" for FR 1 (food + shock) but "reinforcers in conflict" for the one group on FR 10 (food + shock). For another reason, no single descriptive term is entirely satisfactory: The first reinforcer in conflict was not accompanied by punishment (0.00 mA shock level), and the next few would not have been accompanied by punishment if the shock level were not perceptible or high enough to be in some sense aversive. When baseline responding was stable, drug testing began.

Drugs

Buspirone HCl (Bristol-Myers) and chlordiazepoxide HCl (Sigma) were dissolved in isotonic saline and injected PO in a volume of 1 ml/kg of body weight except in Experiment 4, where the route was SC. Pretreatment time was 60 min except in Experiment 5.

Data

Responses per session in VI and reinforcers in each of the four conflict periods were recorded. The values for conflict were summed for the session except where indicated in Experiment 5. Drug tests occurred on Tuesday and Friday, with the previous day serving as control; in some cases, baseline values in conflict showed a trend over time that made using a measure of central tendency inappropriate. Student's *t*-test for dependent samples was applied to the data for each dose as a descriptive statistic.

EXPERIMENT 1: FR 1 VS. FR 10

Most of the multiple schedules of reinforcement and punishment used in the rat to assess the effects of anxiolytics fall into two categories, those similar to the Geller-Seifter test [1960] and those similar to the Davidson-Cook test [Davidson and Cook, 1969; Cook and Davidson, 1973]. The Geller-Seifter schedule is a mult VI 2-min (food) FR 1 (food + shock). The Davidson-Cook schedule is a mult VI 30-sec (food) FR 10 (food + shock) with seven 5-min VI segments and six 2-min punishment segments. Buspirone has failed to produce robust anti-punishment effects on the following schedules: VI 30-sec (food) FR 10 (food + shock) [Amrick and Bennett, 1986; Mason et al., 1987; Sullivan et al., 1983], mult FI 30-sec (food) FR 5 (food + shock) [Gardner, 1986] (FI means fixed-interval), and mult VI 2-min (food) FR 1 (food + shock) (Howard and Pollard, unpublished observation; the shock level was incremental). Buspirone has produced a clear anti-punishment effect in only one study in rat; the schedule was mult VI 1.5-min (food) FR 1 (food + shock) [Young et al., 1987]; the peak effect was only half that of diazepam. In Experiment 1 we compared the effects of buspirone on responding in which every response in FR was rewarded and incrementally punished (conceptually similar to the method of Young et al. [1987]) and responding in which every tenth response in FR was rewarded and incrementally punished.

Method

After acquiring the lever-press response in nightly 15-hr sessions on the progressive ratio schedule, the ovariectomized Long-Evans rats were given three daily 1-hr sessions on the mult VI 2-min FR 1 schedule or five daily 1-hr sessions on the mult VI 2-min FR 10 schedule so that they met the criterion of more than 40 reinforcements in FR (40 responses on FR 1 or 400 on FR 10); that is, they were required to earn an average of more than nine reinforcers in a 3-min FR segment; in previous studies, we had found that the incremental shock for FR 1 reduced the number of responses to about five per conflict period. Median FR 1 reinforcers in the third session was 142 (35.5 per segment, 0.20 responses per sec); mean FR 10 reinforcers in the fifth session was 88 (22 per segment, 1.22 responses per sec). At this point the incremental shock was introduced. Responding in conflict declined abruptly to a low level and in subsequent sessions recovered somewhat. Subjects received approximately 60 sessions of training (with the shockers on) before drugs were given. At this point the subjects on FR 1 (N = 10) were earning a median 19 reinforcers in conflict per session, and those on FR 10 (N = 10) were earning 16.5. Baselines in VI and FR were judged by inspection to be stable. Median body weight was 294 g.

All subjects were injected with chlordiazepoxide 10 mg/kg before each of three sessions in order to habituate them to the drug state [Ts'o and Chenoweth, 1976]. All subjects were injected with saline before one session to provide a vehicle control.

Dose-effect curves were generated in counterbalanced order as follows: Within each group (FR 1 or FR 10) half the subjects received the four doses of buspirone first and the other half received the four doses of chlordiazepoxide first. Within drugs, half the subjects received ascending doses and the other half descending doses. Following the dose-effect determinations, the 5 and 10 mg/kg doses were retested in a similar counterbalanced manner.

Results and Discussion

Figure 1 shows effects of the two drugs on responses in VI and reinforcers in conflict. Chlordiazepoxide produced dose-dependent increases on both parameters in both groups (FR 1 and FR 10). Peak effects, at 20 mg/kg, were as follows (mean values for drug over baseline): for the FR 1 group, VI 1,820/982, conflict 35/20; for the FR 10 group, VI 2652/1386, conflict 27/18. Buspirone, on the other hand, only decreased VI rate. It increased conflict values slightly at 5 mg/kg. Even when subjects with severely depressed VI rates were excluded from calculations, buspirone's peak effect in conflict was less than half that of chlordiazepoxide.

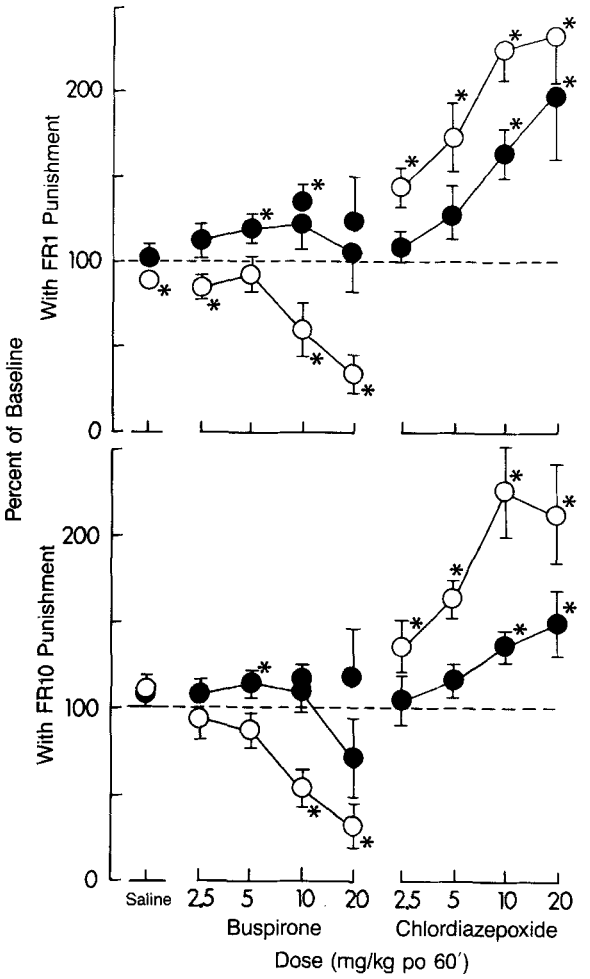

Fig. 1. Effects of buspirone and chlordiazepoxide on VI responding (open symbols) and reinforcers earned in conflict (filled symbols) by drug-experienced hooded rats pressing a lever in a modified Geller-Seifter conflict test with incremental shock. **Upper panel:** Mult VI 2-min (food) FR1 (food + shock). **Lower panel:** Mult VI 2-min (food) FR10 (food + shock). For buspirone, unconnected symbols denote values in conflict for subjects whose unpunished response rate was at least 10% of baseline. * indicates significant difference from baseline, *t*-test, $P < .05$.

Results of the retest of 5 and 10 mg/kg were not materially different from the initial determinations.

We concluded that the FR 10 schedule of food plus incremental shock offers no advantage over the FR 1 schedule for assessing buspirone's anti-punishment effect.

EXPERIMENT 2: DRUG-NAIVE RATS

Patients who had not previously received benzodiazepines were reported to respond better to buspirone than patients who had [Goa and Ward, 1986]. Therefore we tested buspirone's anti-punishment effect in drug-naive rats.

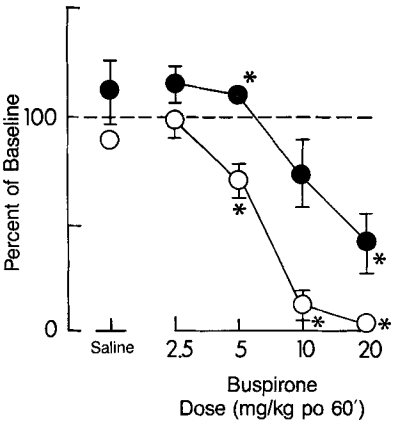

Fig. 2. Effects of buspirone on VI (open symbols) and conflict responding (filled symbols) by otherwise drug-naive hooded rats pressing a lever in a modified Geller-Seifter conflict test with incremental shock [mult VI 2-min (food) FR1 (food + shock)].

Method

The ovariectomized Long-Evans rats were trained essentially the same as the FR 1 group in Experiment 1. They were given 66 sessions on the mult VI 2-min (food) FR 1 (food + shock) schedule. When baselines were stable, the median number of responses in conflict per session was 18.5. Median body weight was 306 g. $N = 9$.

All subjects were injected with saline before one session to provide a vehicle control. The dose-effect curve for buspirone was generated in a counterbalanced order so that half the subjects received ascending doses and the other half received descending doses.

Results and Discussion

Figure 2 shows that buspirone again increased responses in conflict marginally at 5 mg/kg. It only decreased responses in VI.

We concluded that the drug-naive rat offers no advantage over the drug-experienced rat.

EXPERIMENT 3: ALBINO RATS

Albino rats served as subjects in the one published study in which buspirone produced a clear (though modest) increase in punished responding [Young et al., 1987]. To determine whether strain might be an important factor, we generated dose-effect curves for buspirone and chlordiazepoxide in albino rats.

Method

The ovariectomized CD rats were trained essentially the same as the FR 1 group in Experiment 1. They were given 33 sessions on the mult VI 2-min (food) FR 1 (food + shock) schedule, including three sessions following injection of buspirone 10 mg/kg to habituate them to the drug state. All subjects were injected with saline before one session to provide a vehicle control. At this point the median number of responses in conflict per session was 18, and median body weight was 288 g. $N = 10$.

Dose-effect curves were generated in a counterbalanced order as follows: All subjects received buspirone 1.25, 2.5, 5, and 10 mg/kg, half in ascending order and the other half in descending order. Then they were tested with the four doses of chlordiazepoxide similarly

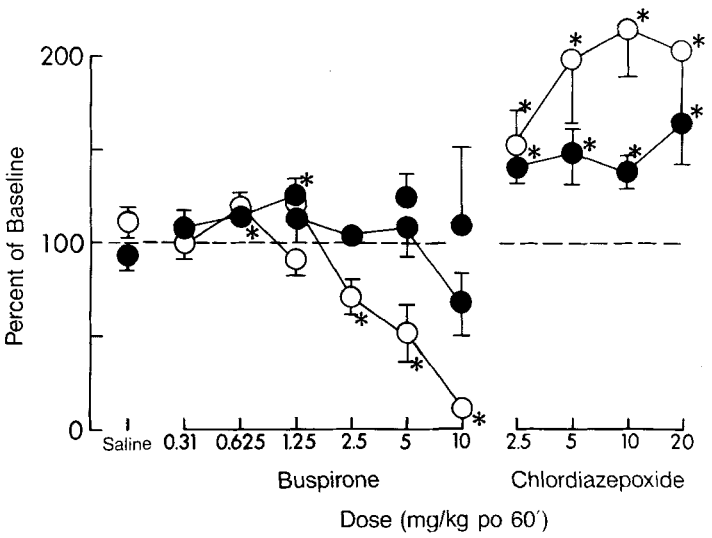

Fig. 3. Effects of buspirone and chlordiazepoxide on VI (open symbols) and conflict responding (filled symbols) by albino rats on the same schedule as that of Figure 2. Buspirone 1.25–10 mg/kg were tested first, then 0.31–1.25 mg/kg. Unconnected symbols are as in Figure 1.

counterbalanced. About 2 weeks later, they were tested with buspirone 0.31, 0.625, and again 1.25 mg/kg, similarly counterbalanced.

Results and Discussion

Figure 3 shows that chlordiazepoxide had its typical rate-increasing effect on VI and conflict responding, while buspirone increased conflict responding only marginally at 0.625 mg/kg and in one test of 1.25 mg/kg. Buspirone's depressant effect occurred at a lower dose in the albino rats than in the hooded rats used in Experiments 1 and 2.

We concluded that the albino rat offers no advantage over the hooded rat.

EXPERIMENT 4: SC INJECTION

In three of the four cited studies in which buspirone was injected SC (Table 1), there was some positive effect [Pich and Samanin, 1986; Schreur, 1988; Kehne et al., 1988]. To determine whether route of administration might be an important factor, we generated a dose-effect curve for buspirone injected SC.

Method

The subjects from Experiment 3 were used, and other particulars except injection procedure remained the same. Buspirone was tested at 1.0 and 0.1 mg/kg SC, after which the experiment was suspended for 7 weeks, during which the subjects were maintained on 2-hr access to food each day. After running was resumed and baselines were stable, all subjects received buspirone 0.0, 0.5, 1.0, 2.0, and 4.0 mg/kg SC, half in ascending order and the other half in descending order. $N = 9$.

Results and Discussion

Figure 4 shows that buspirone 1.0 mg/kg SC increased responses in conflict slightly in one of two determinations. All doses from 0.5 to 4.0 mg/kg decreased VI responding.

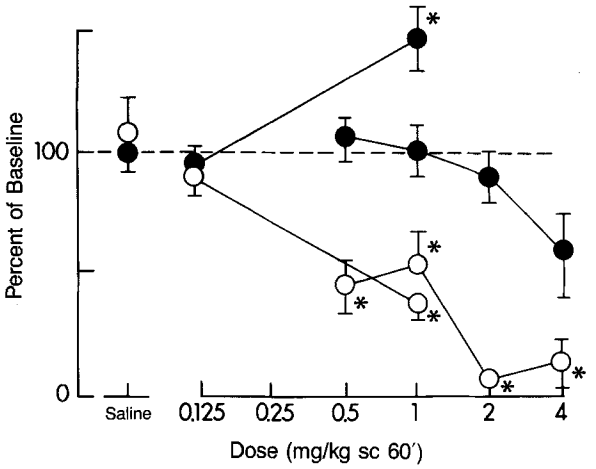

Fig. 4. Effects of buspirone injected SC on VI (open symbols) and conflict responding (filled symbols) by rats on the same schedule as that of Figure 2; 0.1 and 1 mg/kg were tested first, then 0.5–4.0 mg/kg.

We concluded that SC administration offers no advantage over PO administration, although the compound appears to be more potent SC.

EXPERIMENT 5: TIME COURSE

Wherever buspirone shows a positive effect in Table 1, the pretreatment time is 30 min or less. To determine whether a pretreatment time shorter than 60 min or a finer grain of analysis than that of Experiments 1–4 might reveal an anti-punishment effect, we generated dose-effect curves for chlordiazepoxide and buspirone by sampling data every 15 min over a 2-hr session.

Method

A group of ovariectomized Long-Evans rats with a history of training and drug testing on the mult VI 2-min (food) FR 1 (food + shock) schedule were used. The regimen was the same as in the earlier experiments except that the subjects were given two 1-hr sessions back-to-back daily—in effect a 2-hr session with eight 3-min conflict periods on 15-min centers. On the first 3 treatment days (Tuesdays and Fridays), all subjects received the same treatment, chlordiazepoxide 10, 5, and 20 mg/kg, to establish the robustness of effect of a standard anxiolytic in single 3-min conflict periods. On the fourth treatment day, all subjects were injected with saline to provide a vehicle control. Then the dose-effect curve for buspirone was generated in a counterbalanced order so that half the subjects received ascending doses and the other half received descending doses. $N = 8–11$ (some baselines went awry and some data were lost because of malfunctions).

Results and Discussion

Figure 5 shows the number of responses in each 3-min conflict period (i.e., at 15-min intervals) during the 2-hr sessions on baseline and drug days. Although single-period bins yielded somewhat variable baseline data, chlordiazepoxide reliably and dose-dependently increased responses in conflict. Buspirone, on the other hand, produced only small, scattered increases, with no pattern. The higher doses of buspirone tended to decrease responses in the first conflict period, which occurred 15 min after injection; this was probably the result of a

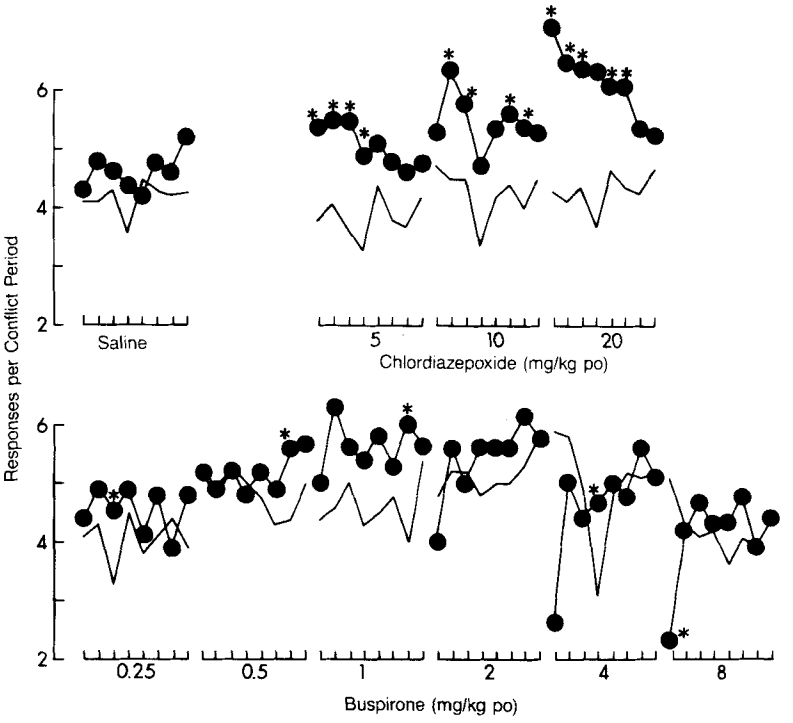

Fig. 5. Effects of chlordiazepoxide and buspirone on responses in each of eight 3-min conflict periods during 2-hr sessions—i.e., at 15-min intervals. The schedule was the same as that of Figure 2. A data point on the plain curve represents number of responses in conflict on the previous (baseline) day; a filled symbol represents this value on the drug day.

general decrease in responding, because 4 and 8 mg/kg significantly decreased VI responding in the first and second hours. (Our equipment was not programmed to measure VI responding at shorter time periods.)

We concluded that the more finely grained analysis with respect to time after injection offers no advantage in revealing an anti-punishment effect of buspirone.

GENERAL DISCUSSION

These results confirm and extend the results of the few published studies on the effects of buspirone upon punished lever-pressing in the rat. None of the variations we tested—larger FR value in the punishment component, drug-naive subjects, different strain, SC injection, finer-grained time course—revealed robust anti-conflict activity.

No well-validated behavioral predictor of anxiolysis has been shown to identify buspirone (see Table 1). The clearest results to date have come from punished key-pecking in the pigeon; if these results are replicated in another laboratory, and a broad array of non-anxiolytics has been tested under similar conditions to strengthen specificity, punished key-pecking in the pigeon could become the behavioral method of choice for identifying anxiolytics. Social interaction shows enough promise to warrant further development, as does potentiated startle.

Conditioned defensive burying has been proposed as a drug-class-specific screening method for anxiolytics [Treit, 1985]. Conventional anxiolytics reduce the degree to which a rat will cover an electrified probe with bedding. We were unable to show a reduction in burying

with buspirone 8–64 mg/kg [Craft et al., 1988]. However, using refined methodology, Treit has recently shown that doses of 0.1, 0.5, and 1.0 mg/kg SC reduce burying without altering general activity [Treit and Fundytus, 1988]. This test deserves further attention.

The fact that buspirone has its clinical effect only after chronic treatment, whereas conventional anxiolytics work acutely, may be critical for the selection of behavioral methods to identify novel buspirone-like anxiolytics and to explore the mechanisms of anxiolysis. Expecting compounds with delayed onset of therapeutic activity to be registered by methods designed to identify acutely active compounds may be unrealistic. It seems likely that such methods, if they register positive for buspirone and similar compounds, may be registering a side effect, an epiphenomenon. On the other hand, if a method is accurate at the empirical level—if it identifies compounds of a specific therapeutic class without having any other known relevance to the disease—then it is useful in the drug-screening laboratory.

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