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Acute and Chronic Administration of Buspirone Fails to Yield Anxiolytic-Like Effects in a Mouse Operant Punishment Paradigm

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MARTIN, J. R., J.-L. MOREAU, F. JENCK AND R. CUMIN. *Acute and chronic administration of buspirone fails to yield anxiolytic-like effects in a mouse operant punishment paradigm.* PHARMACOL BIOCHEM BEHAV 46(4) 905–910, 1993.—Drug-naive mice failed to exhibit antipunishment effects of ascending doses of buspirone (1–30 mg/kg, PO) in an operant punishment paradigm; however, these same mice subsequently exhibited increased punished responding after diazepam (10 mg/kg, PO). In a separate group of drug-naive mice, diazepam (1–30 mg/kg, PO) produced a robust antipunishment effect under identical experimental conditions, but crossover to buspirone (10 mg/kg, PO) failed to enhance punished responding. In a further experiment using this conflict model, two groups of benzodiazepine-experienced mice received daily oral administration of either vehicle or buspirone (5 mg/kg) for four weeks followed by a test with buspirone; neither group exhibited an antipunishment effect. Two other groups of benzodiazepine-experienced mice received either oral vehicle or diazepam (5 mg/kg) daily for four weeks followed by a test with diazepam; both groups exhibited a clear antipunishment effect. Finally, a group of benzodiazepine-experienced mice given vehicle daily for four weeks followed by a test with vehicle failed to exhibit an antipunishment effect. Thus, despite the attempt to optimize some important experimental conditions in this mouse conflict paradigm, buspirone still failed to produce an antipunishment effect. In contrast, diazepam consistently exhibited a robust anxiolytic-like effect under the same experimental conditions.

Anxiety Conflict Drug-naive and drug-experienced mice Operant punishment paradigm
Buspirone Diazepam

THE azaspirodecanedione derivative buspirone has been found to reduce symptoms of generalized anxiety (12). In contrast to many of the commonly used tranquillizers, buspirone does not appear to produce its anxiolytic effect by interaction with benzodiazepine receptors (28,38), but instead has been hypothesized to act primarily via 5-HT_{1A} receptor agonism (23,40). For this reason, the pharmacological profile of buspirone has been of considerable scientific interest. Particularly interesting is the difficulty in consistently obtaining robust anxiolytic-like effects with buspirone in operant punishment paradigms in animals, in apparent contrast to conventional anxiolytics such as benzodiazepines, barbiturates, and propanediol carbamates (cf. 25).

In Geller–Seifter type conflict tasks involving lever-pressing for food reinforcement under contingent shock conditions, the effects of buspirone have been inconsistent (for review see 25). Some results obtained in such tests in monkeys (9,38) and rats (9,15,42) suggest that buspirone increases punished responding, but no confirmation was obtained from other investigations in these species which found at most only marginal antipunishment effects (8,11,13,18,36,39). Furthermore, in an extensive parametric investigation in rats, buspirone failed to produce any antipunishment effects under a wide variety of experimental conditions (25). There is, however, evidence that buspirone is effective in rats in disinhibiting food-reinforced responding suppressed during a stimulus that terminated with an unavoidable shock (29,30). Interestingly, buspirone increased punished key-pecking in the pigeon in a robust manner reminiscent of the effects obtained with benzodiazepine receptor agonists, suggesting the possible importance of species differences (2,3,21). In conflict tests involving the disinhibition of unconditioned or conditioned shock-induced suppression of drinking, a number of studies have reported that acute administration of buspirone enhanced punished drinking (7,14,19,20,22,24,27,28,34,37,38), but the active dose ranges were narrow and often discrepant among studies and, furthermore, other investigations have failed to replicate the effect (6,8,13,31,36). Schefke et al. (32) has reported that chronic treatment with buspirone was much more effective than acute administration in enhancing punished

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drinking. Finally, buspirone has been evaluated in a variety of other test paradigms which remain to be as extensively validated as the operant punishment model but which have been suggested to be predictive of anxiolytic activity in man [although, again, with mixed results (cf. 25)].

Although buspirone has not been evaluated yet in mice in an operant punishment paradigm, it has been reported to enhance exploration by mice of the illuminated side of a two-compartment light–dark apparatus (5,41). In the present investigation, an attempt was made to maximize the likelihood of detecting any potential antipunishment activity of buspirone in an operant punishment task in mice, a paradigm which has previously proved useful in demonstrating the antipunishment activity of compounds which act via benzodiazepine receptors (26,35). The animals were treated orally with an ascending series of drug doses, with each dose given once weekly for three successive weeks beginning with a low dose based upon literature results. Vehicle was evaluated on test days interspersed among the drug evaluation days to provide a baseline which extended throughout the experiment. Diazepam was included in both experiments as a positive control. Furthermore, a partial crossover design was used to evaluate the effects of buspirone and diazepam on both punished and unpunished responding in the same animals. In view of the report that patients receiving buspirone for the management of anxiety exhibited clearer improvement when they had not previously been treated with benzodiazepines (33), it was considered important to begin the crossover experiment with drug-naive mice. Finally, clinical effects of buspirone have been reported to have a delayed onset of up to one to two weeks (12), and thus in a second experiment drug-experienced mice received repeated daily buspirone or vehicle treatment for four weeks prior to the evaluation of buspirone in the operant punishment paradigm.

METHOD

Animals and Maintenance Conditions

The female albino mice used (Ibm: MORO; Biological Research Laboratories, 4414 Füllinsdorf, Switzerland) were several months old and had previously been well trained in this operant punishment task. The mice were individually housed in Macrolon type 1 plastic cages (ca. 13 × 23 × 13 cm) with sawdust bedding. Tap water was available ad lib, whereas access to the laboratory chow (No. 850; NAF AG, Gossau, St. Gallen, Switzerland) was restricted so as to maintain the mice at approximately 80–85% of their free-feeding body weight based on the expected growth curve. The animal quarters were maintained on a 12 : 12-h light–dark cycle with light onset at 0600. Room temperature (21–23°C) and humidity (55–65%) were regulated.

Training

The test method was a modification of procedures which were designed to evaluate the disinhibiting effects of experimental substances on responding in rats and mice which was suppressed to a considerable degree by response-contingent mild foot shock (10,26).

Food-deprived mice were first trained to press a lever in a sound-attenuated operant box (ca. 17 × 18 × 21 cm) to receive a 20-mg food pellet (Formula A/I; P.J. Noyes, Inc., Lancaster, NH). Training sessions were 20 min and were given on several days each week. Once stable food-reinforced lever-pressing was established, a new test phase was introduced for one to two sessions per week. In these sessions (conflict test), an initial 5-min period during which each lever press was reinforced with a food pellet was followed by an unsignaled 15-min period during which each lever press resulted in both a mild 300-ms scrambled shock delivered through the grid floor and concomitant delivery of a food pellet. The shock level was usually 0.2 mA but was sometimes increased enough to ensure a low baseline level of responding. In a preliminary experiment done using other groups of similar mice trained in this conflict procedure, neither buspirone (3, 10, or 30 mg/kg) nor diazepam (3, 10, or 30 mg/kg) given orally 30 min prior to testing was found to affect reactivity to foot shock (0, 0.1, 0.2, 0.3, 0.4 mA) in the test apparatus used in this investigation or to affect latency to lick the forepaws in a standard hot plate test for analgesia. Drug-naive mice were used in Experiment 1. The mice used in Experiment 2 had previously received treatment with oral anxiolytic doses of diazepam prior to the start of the experiment. This ensured that each of these mice had been demonstrated to exhibit robust drug-induced anxiolytic effects in this test paradigm before selection for use in Experiment 2.

Test Procedure

Behavioral testing was done between 0700 and 1700. Typically, the mice received training sessions (i.e., a 20-min session during which responding resulted in food reinforcement but never shock) on Mondays, Wednesdays, and Fridays. On Tuesdays and Thursdays the mice were tested in the previously described conflict task (i.e., an initial 5-min period in which responding was food-reinforced followed by a 15-min period during which each response resulted in both food and shock). In these conflict tests both unpunished and punished responding was measured. Vehicle was usually given on Tuesdays and drug on Thursdays. Successive drug exposures were thus carried out at one-week intervals. Treatment was orally administered approximately 0.5 h prior to testing.

In the first experiment a partial crossover design was used with half of the drug-naive mice first receiving ascending doses of buspirone (buspirone–diazepam group; $N = 12$; 1, 3, 10, and 30 mg/kg) followed by a one-week washout period and then subsequently 10 mg/kg diazepam. The remaining mice first received ascending doses of diazepam (diazepam–buspirone group; $N = 11$; 1, 3, 10, and 30 mg/kg) followed by a one-week washout period and then subsequently 10 mg/kg buspirone.

In a second experiment, the effect of daily oral administration of buspirone (B; 5 mg/kg), diazepam (D; 5 mg/kg), or vehicle (V) for four weeks were evaluated on unpunished and punished responding in benzodiazepine-experienced mice in a conflict test given 0.5 h after administration of vehicle, buspirone, or diazepam on day 29. Comparison was made to a conflict test done after oral vehicle administration prior to the start of the subchronic treatment regimen. The combinations of four-week treatment and final drug administration were VV, VB, BB, VD, and DD done in separate groups of 15 mice each.

Preparation of Drugs

The experimental compounds buspirone and diazepam were administered orally in a vehicle of 0.3% (v/v) Tween 80 in distilled water. The volume administered was 5 ml/kg body weight.

Data Analysis

Both unpunished (i.e., the initial 5-min period) and punished (i.e., the subsequent 15-min period involving concomitant food and shock delivery) phases of the conflict test session were evaluated for each drug dose. Since there was no apparent trend in the results for either unpunished or punished responding from the first to the third weekly test, the mean value for the three tests carried out at each dose was used in the statistical analysis. The data on unpunished and punished responding were analyzed for each individual dose condition in comparison to the mean vehicle value (mean of all vehicle data). A two-tailed Wilcoxon matched-pairs, signed-ranks test was used with a p value of 0.05 or less accepted as statistically significant.

RESULTS

Experiment 1: Partial Crossover Design for Buspirone and Diazepam

Buspirone and diazepam were evaluated in two separate groups of drug-naive mice in an identical series of ascending doses (1, 3, 10, and 30 mg/kg). Following a washout period, the crossover consisted of evaluation of only a single dose of the other compound (10 mg/kg). Each dose condition was tested once each week for three successive weeks.

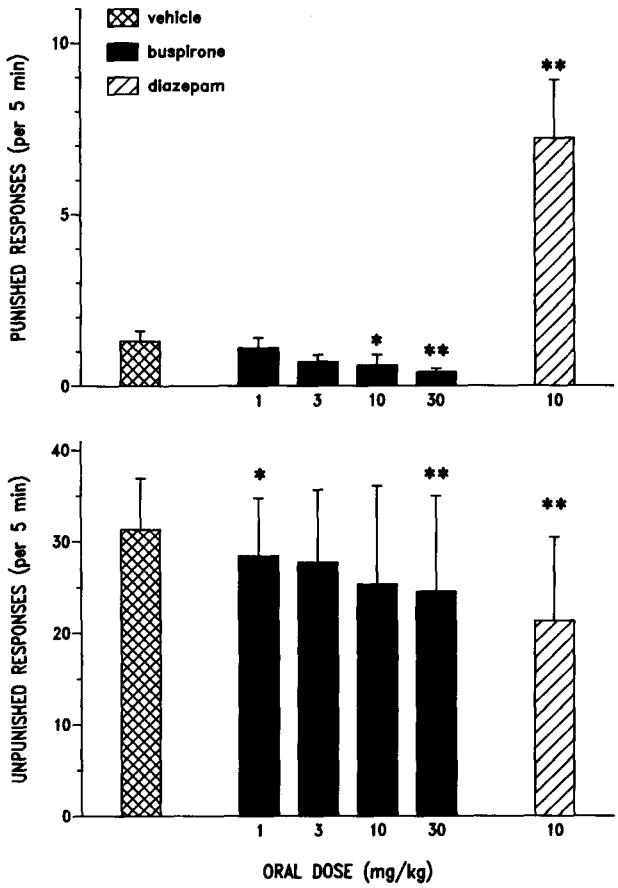

FIG. 1. Mean number of punished lever-press responses per 5 min (with the standard deviation) in an operant punishment paradigm following oral administration of a succession of ascending doses of buspirone followed by a washout period and then a single dose of diazepam. *$P < 0.05$ and **$P < 0.01$ in comparison with the mean for the vehicle condition using a two-tailed Wilcoxon test.

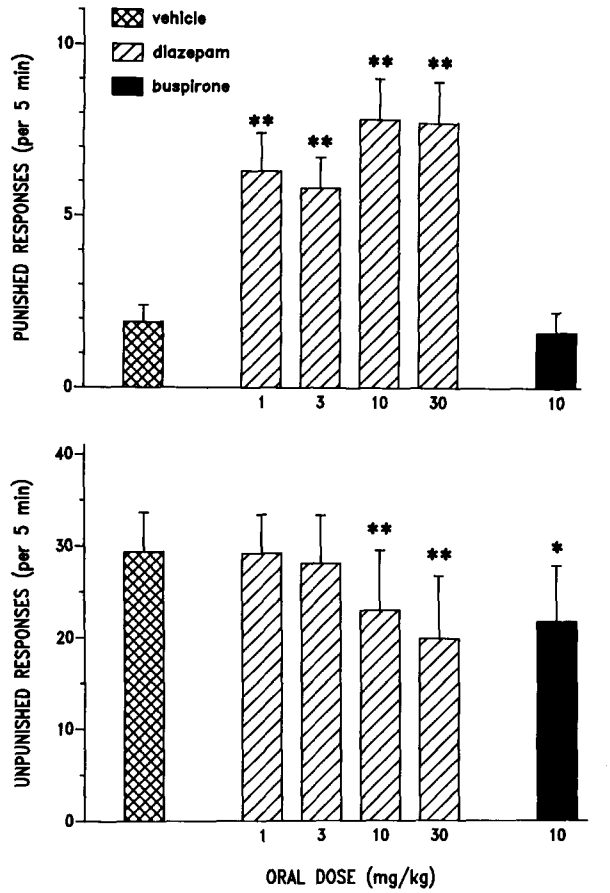

FIG. 2. Mean number of punished lever-press responses per 5 min (with the standard deviation) in an operant punishment paradigm following oral administration of a succession of ascending doses of diazepam followed by a washout period and then a single dose of buspirone. *$P < 0.05$ and **$P < 0.01$ in comparison with the mean for the vehicle condition using a two-tailed Wilcoxon test.

The results on punished and unpunished responding for the buspirone–diazepam group are illustrated in Fig. 1. In the conflict task, the mice of the buspirone–diazepam group (N = 12) in fact exhibited less punished responding after each of the buspirone doses than after vehicle; this difference reached statistical significance for doses of 10 and 30 mg/kg. Furthermore, at the dose 3 mg/kg and above, buspirone reduced punished responding compared to the vehicle baseline in 9 or more of the 12 mice. Similarly, unpunished responding was reduced at all buspirone doses, but statistical significance was only reached at 1 and 30 mg/kg; at least 9 out of the 12 mice exhibited lower response rates after all doses of buspirone than after vehicle. In this partial crossover design, the single dose 10 mg/kg diazepam was subsequently administered to these same mice after a washout period and was found to significantly enhance punished responding (5.5-fold increase) and concomitantly significantly reduce unpunished responding (−32%); 10 out of the 12 mice exhibited more punished responding after diazepam than after vehicle, and 11 from 12 mice showed reduced unpunished responding after diazepam compared to vehicle.

The results on punished and unpunished responding for the diazepam-buspirone group are illustrated in Fig. 2. The mice from the diazepam-buspirone group (N = 11) exhibited significantly more punished responding (a three- to fourfold increase) after each of the diazepam doses (1, 3, 10 and 30 mg/kg) than after vehicle, with at least 10 out of the 11 mice exhibiting more punished responding after diazepam than after vehicle. Unpunished responding was significantly reduced by diazepam relative to the vehicle baseline at the doses 10 and 30 mg/kg (−22% and −32%, respectively), with 10 from the 11 mice exhibiting less unpunished responding after each of these two doses of diazepam than after vehicle. Following a washout period, a single dose of buspirone (10 mg/kg) was evaluated. Buspirone actually nonsignificantly reduced punished responding compared to vehicle (−16%), with 8 from the 11 mice exhibiting less punished responding after buspirone than after vehicle. Unpunished responding was significantly reduced by buspirone (−26%), with 10 out of the 11 benzodiazepine-experienced mice exhibiting less unpunished responding after buspirone than these same mice exhibited after vehicle.

Experiment 2: Effects of Buspirone and Diazepam After Subchronic Treatment

In all five treatment groups (Ns = 15), prior to the start of the four-week treatment phase, punished and unpunished responding were evaluated in the conflict paradigm 0.5 h after vehicle administration (PRE). This provided the baseline for subsequent statistical comparison. The different groups of benzodiazepine-experienced mice then received four-week oral treatment with buspirone (B; 5 mg/kg), diazepam (D; 5 mg/kg), or vehicle (V), with a conflict test done on the 29th day 0.5 h after administration of vehicle, buspirone, or diazepam. The treatment combinations of subchronic treatment and final drug administration were VV, VB, BB, VD and DD.

Regardless of whether mice had been subchronically treated with vehicle or diazepam, administration of 5 mg/kg diazepam significantly enhanced punished responding relative to the vehicle baseline (PRE) by a factor of seven- to eightfold without any concomitant reduction of unpunished responding. In contrast, in mice which had been subchronically treated with vehicle or buspirone, administration of 5 mg/kg buspirone failed to significantly affect punished responding relative to the vehicle baseline (PRE). However, unpunished responding was significantly reduced by 5 mg/kg buspirone in the group which had previously received subchronic treatment with vehicle (−32%) but not in that which had received subchronic treatment with buspirone (−6%). Subchronic treatment with vehicle did not alter punished or unpunished responding measured after vehicle administration on day 29 in comparison to the vehicle baseline (PRE). These results are summarized in Table 1.

DISCUSSION

Buspirone, which has been introduced into clinical practice for therapy of generalized anxiety disorder, has been demonstrated only inconsistently to exhibit clear antipunishment effects in operant tasks in animals (which are hypothesized to be predictive of anxiolytic activity in man). This is in marked contrast to the well-established activity of benzodiazepine receptor agonists or partial agonists in operant punishment paradigms. It has been suggested that the model itself might be insensitive to the anxiolytic effects of drugs differing from the classical benzodiazepine anxiolytics; however, the experimental conditions used in the investigation of the antipunishment effects of buspirone in animals have not always been ideal. From clinical investigations, it is known that there is a delay in the onset of the anxiolytic effect of buspirone of about one to two weeks (12), and furthermore, prior experience with benzodiazepine tranquillizers appears to reduce subsequent

TABLE 1

EFFECTS OF BUSPIRONE AND DIAZEPAM ON PUNISHED AND UNPUNISHED RESPONDING IN MICE FOLLOWING FOUR-WEEK TREATMENT WITH VEHICLE, BUSPIRONE, OR DIAZEPAM

Group (Four-Week Treatment)	Treatment in Test Session	Mean Responses per 5 Min (± SD) Punished Responses	Unpunished Responses
Group 1: Vehicle	Vehicle Baseline	1.6 ± 2.6	38.1 ± 12.6
	Vehicle on Day 29	0.9 ± 0.9	38.5 ± 13.1
Group 2: Vehicle	Vehicle Baseline	0.7 ± 0.4	46.3 ± 17.6
	Diazepam on Day 29	5.2 ± 6.5*	38.4 ± 14.2
Group 3: Diazepam	Vehicle Baseline	1.4 ± 2.2	39.9 ± 14.3
	Diazepam on Day 29	11.5 ± 8.6*	41.2 ± 9.4
Group 4: Vehicle	Vehicle Baseline	1.9 ± 2.5	47.3 ± 17.3
	Buspirone on Day 29	1.9 ± 4.7	32.1 ± 18.1†
Group 5: Buspirone	Vehicle Baseline	1.5 ± 1.5	43.9 ± 10.4
	Buspirone on Day 29	1.6 ± 3.0	41.1 ± 17.2

Prior to the start of the 28-day period of treatment, each mouse was tested in the conflict task after vehicle administration to provide a baseline. Following the subchronic treatment regimen, each mouse was tested again 0.5 h after administration of vehicle, buspirone, or diazepam on day 29.

*$p < 0.01$ and †$p < 0.05$ for the statistical comparison with the vehicle baseline for the same group done with a two-tailed Wilcoxon test.

success with buspirone therapy (33). The present investigation in mice attempted to take such experimental factors into account. In addition, in view of the very poor agreement concerning the active dose range for buspirone, it was also necessary to evaluate a wide dose range, with each dose administered several times.

In the first experiment, drug-naive mice were tested in a partial crossover design in which a series of ascending doses of buspirone and diazepam were administered in the first phase of the experiment, and following washout, a single dose of the other compound was evaluated. All doses of diazepam either preceding or following buspirone treatment significantly enhanced punished responding. In contrast, none of the buspirone doses either preceding (i.e., the condition under which buspirone would be hypothesized to exhibit the best anxiolytic effect) or following diazepam treatment increased punished responding. Unpunished responding was significantly decreased by 10 and 30 mg/kg diazepam and by 1, 10, and 30 mg/kg buspirone regardless of when these doses were evaluated within the crossover design. These results were quite similar to those obtained previously in a complete crossover experiment that was carried out under the same experimental conditions with buspirone (1, 3, 10, 30, and 60 mg/kg, PO) and diazepam (10, 15, 20, 30, and 60 mg/kg, PO), but using only six to eight mice per dose (results not shown).

In a further experiment, groups of benzodiazepine-experienced mice received four-week oral daily administration of vehicle, 5 mg/kg buspirone, or 5 mg/kg diazepam. At the end of the subchronic regimen, an oral administration of either vehicle, 5 mg/kg buspirone, or 5 mg/kg diazepam was given on day 29, followed by a conflict test. Comparison for each treatment group was made with a vehicle control done prior to the start of the subchronic regimen. Regardless of whether subchronic treatment was vehicle or buspirone, a final administration of buspirone failed to produce an antipunishment effect (unpunished responding was reduced in the former group). In contrast, regardless of whether subchronic treatment was vehicle or diazepam, a final administration of diazepam significantly increased punished responding (unpunished responding was unaffected). The control group which received subchronic treatment with vehicle and was then given a final administration of vehicle failed to exhibit any effects on either punished or unpunished responding compared to baseline.

Despite these attempts to optimize some of the experimental parameters so as to facilitate the detection of any potential antipunishment effect of buspirone in mice, no such anxiolytic-like effect was observed, even when the buspirone dose range extended up to doses high enough to reduce unpunished responding. These results are consistent with those observed in rats and monkeys (but contrast with the observation of clear antipunishment effects of buspirone, as well as benzodiazepine receptor agonists, in operant punishment tasks in pigeons). Thus, neither the use of drug-naive animals in a crossover design nor subchronic treatment with buspirone in the present investigation resulted in any evidence for an antipunishment effect in an operant punishment task in mice. In contrast, the positive control substance diazepam was consistently shown to exert a dramatic antipunishment effect, thus clearly indicating that this mouse conflict model itself is sensitive to this classical effect of benzodiazepine anxiolytics. It is interesting to note that in experiments using rats [for method see (17)] buspirone significantly enhanced consumption of palatable food at the oral doses 0.3 (20%), 1 (12%), 3 (21%), and 10 mg/kg (20%), but was ineffective at 0.1 (4%) and 30 mg/kg (−10%); diazepam significantly increased food intake in two experiments at the doses 1 (28%), 3 (40%), 10 (41%), and 30 mg/kg (40%). With respect to anxiolytic-like activity in an operant conflict paradigm [for method see (17)] in rats of the same sex, age, and strain as those tested for palatable food intake, buspirone failed to enhance punished responding at the doses 1 to 30 mg/kg PO, whereas diazepam significantly increased punished responding at 2–30 mg/kg PO. Even within the dose range of the lowest anxiolytic dose of diazepam, there was a greater hyperphagic effect than at any of the doses of buspirone tested (all of which failed to induce a significant anxiolytic-like effect). Thus the greater disinhibition of feeding observed for diazepam compared to buspirone appears to be consistent with the greater disinhibition of punished responding also observed for the former compound.

It is possible that the anxiolytic effect of buspirone which has been demonstrated in patients may critically depend on neuroleptic effects as have been demonstrated in animals (1), especially in light of the clinical use of neuroleptics in the treatment of generalized anxiety. However, it has proved difficult to detect any anxiolytic-like activity of classical neuroleptics in the operant conflict paradigm in animals (e.g., 4). Alternatively, it has often been suggested that anxiolytics acting by mechanisms of action other than GABA modulation may not be readily detected in the operant punishment paradigm, a task which was originally developed using benzodiazepines.

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