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Inverse Agonist Properties of the FG 7142 Discriminative Stimulus

NANCY J. LEIDENHEIMER[1] AND MARTIN D. SCHECHTER

Department of Pharmacology, Northeastern Ohio Universities College of Medicine, Rootstown, OH 44272

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LEIDENHEIMER, N. J. AND M. D. SCHECHTER. *Inverse agonist properties of the FG 7142 discriminative stimulus.* PHARMACOL BIOCHEM BEHAV **38**(1) 99–104, 1991.—A two-lever, food-motivated discrimination was established between the benzodiazepine receptor partial inverse agonist FG 7142 (5.0 mg/kg) and its vehicle. The FG 7142 discriminative stimulus was pharmacologically characterized by testing trained rats with a variety of benzodiazepine receptor ligands. Administration of the inverse agonist DMCM (0.15–0.30 mg/kg) dose-dependently mimicked the FG 7142 stimulus. In contrast, the benzodiazepine receptor agonist chlordiazepoxide, partial agonist ZK 91 296, mixed agonist/antagonist CGS 9896 and antagonist RO 15-1788 blocked the FG 7142 cue. These results indicate that the FG 7142 discriminative stimulus is based on its inverse agonist activity. The generalization of FG 7142 to the anxiogenic/convulsant compound pentylenetetrazole (PTZ), but not to the anorectic agent norfenfluramine, indicates that the anxiogenic properties of FG 7142, rather than its anorectic actions, may underlie the FG 7142 discriminative stimulus.

Drug discrimination FG 7142 Stimulus properties of drugs Benzodiazepine receptor Anxiety Inverse agonist DMCM Rats PTZ

FG 7142 is a β-carboline which acts as a benzodiazepine receptor partial inverse agonist to negatively modulate $GABA_A$ receptor mediated Cl^- conductance (11, 21, 31). Behaviorally, FG 7142 possesses anxiogenic (7, 9, 22, 25, 30, 34), proconvulsant (8, 16, 17) and anorectic (4,5) properties. Recently, FG 7142 has been shown to be capable of controlling differential responding in the drug discrimination paradigm (14). The FG 7142-controlled stimulus generalized to a physiological stressor suggesting that the FG 7142 discriminative cue is anxiomimetic in nature. FG 7142 has also been tested in rats trained to discriminate other compounds. Rats trained to discriminate the inverse agonist DMCM (19) or anxiogenic/convulsant pentylenetetrazole (PTZ) (31,32) from vehicle responded predominately on the drug-appropriate lever following FG 7142 administration. Additionally, FG 7142 antagonized the discriminative stimulus produced by the benzodiazepine receptor agonist chlordiazepoxide (31,32). These results indicate that the FG 7142 discriminative stimulus is related to its inverse agonist properties. However, the FG 7142-controlled discrimination has not yet been characterized pharmacologically. The purpose of the present experiments was to characterize an FG 7142-controlled discrimination with benzodiazepine receptor ligands and to further assess the behavioral nature of the FG 7142 discriminative stimulus.

METHOD

Subjects

The group of animals trained to discriminate FG 7142 in the present study were nine experimentally naive male Sprague-Dawley rats purchased from the Zivic-Miller Laboratories (Allison Park, PA). They weighed 125–250 g at the beginning of the experiment and were individually housed and maintained on a 12-h light (0600–1800)/12-h dark cycle in a room kept at temperatures between 20–22°C. They had access to water ad lib and were given a daily rationing of commercial rat chow. This feeding regimen was adjusted to maintain their body weights at approximately 85% of the weight that would be expected to be attained by rats of the same age given food ad lib. This rationing of food provided motivation to learn the appetitive task. In addition to this group of rats, another group of rats (n = 8) previously trained to discriminate FG 7142 (5.0 mg/kg) from vehicle (14) was used in this study. These rats were obtained from the same supplier and were cared for in an identical manner.

Apparatus

Twelve standard rodent operant chambers (Lafayette Instruments Corporation, Lafayette, IN) were used as the experimental space. Each chamber contained two levers situated 7 cm apart and 7 cm above a grid floor. A food receptacle was located 2 cm above the grid floor, midway between the two levers. Each operant chamber was enclosed in an unlit sound-attenuated cubicle with an exhaust fan for ventilation. Solid-state programming equipment (Med Associates, E. Fairfield, VT), located in an adjacent room, was used to control and record discrimination sessions.

Training Procedure

A detailed protocol of the training procedure has been pub-

[1]Requests for reprints should be addressed to Dr. Nancy J. Leidenheimer, Department of Pharmacology, University of Colorado Health Sciences Center, Denver, CO 80262.

lished (13). Briefly, rats were trained to discriminate FG 7142 (5.0 mg/kg) from vehicle (V) in a two-lever, food-motivated operant task. Prior to the initiation of the training, one lever in the operant chamber was designated as the vehicle lever and the other lever was designated as the FG 7142 lever. Thirty min prior to each training session the food-deprived rats received an IP injection (1 ml/kg volume) of either FG 7142 (5.0 mg/kg) or V. After FG 7142 administration, responses on the FG 7142 lever resulted in food reinforcement, whereas responses on the vehicle lever had no programmed consequence. Following vehicle administration, responses on the vehicle lever produced reinforcement, while responses on the FG 7142 lever did not produce reinforcement. The reinforcement schedule was set at a fixed ratio of ten (FR 10), i.e., ten injection-appropriate lever responses yielded one reinforcement (45 mg Noyes pellet). This reinforcement schedule was attained by beginning on an FR 1 schedule and gradually increasing the reinforcement requirements over five days. Once the FR 10 schedule was attained, daily training sessions were conducted until animals had made 400 injection-appropriate responses. Training sessions were conducted once per day according to the following two-week training schedule: FG,V,V,FG,FG; V,FG,FG,V,V. The lever which was pressed ten times first in the session was considered to be the selected lever for that session. For each animal, the training schedule was repeated until the selected lever was injection-appropriate in 8 out of 10 consecutive training sessions, twice. Data collection began when all animals had fulfilled this criterion.

Dose-Response Experiments

Once discriminative criterion was attained, the discrimination training regimen was limited to every other day in order to maintain the discrimination. Between FG 7142 and vehicle maintenance days, rats were tested with varying doses of FG 7142 such that each dose was tested twice, once following an FG 7142 maintenance (FGM) day and once following a vehicle maintenance (VM) day according to the following schedule: FGM, FG dose 1, VM, FG dose 1; FGM, FG dose 2, VM, FG dose 2, etc. This counterbalancing was used to control for any possible residual influence from the previous maintenance day. Thirty min following FG 7142 administration, the rats were placed into the operant chamber and immediately removed, without receiving reinforcement, following the tenth response on either lever. Animals were not reinforced on test days to preclude any possible training to a dose of FG 7142 different than that used in training/maintenance. Responses on both the drug and vehicle levers were, however, recorded and used to calculate the quantitative measurement (see the Measurements and Statistics section, below).

Generalization Experiments

Novel test drugs were administered to rats to determine if the interoceptive cue produced by the novel test drug was similar or dissimilar to that produced by FG 7142. Each dose of novel drug (ND) that was tested was counterbalanced between FG 7142 maintenance (FGM) and vehicle maintenance (VM) days by employing the following schedule: FGM, ND dose 1, VM, ND dose 1; FGM, ND dose 2, VM, ND dose 2, etc. On test days animals were removed from the discrimination chamber, without reinforcement, upon emitting ten responses on either lever. Responses on both the FG 7142 and vehicle levers were each recorded. Dose and treatment times were determined from the literature. DMCM (31) and pentylenetetrazole (PTZ) (13) were administered 30 minutes prior to discrimination sessions, whereas norfenfluramine (28) was administered 20 min prior to the session.

Antagonism Experiments

Rats were coadministered FG 7142 and the antagonist drug at times described below and placed into the discrimination chamber. Upon emitting ten responses on either lever, the animals were immediately removed from the discrimination chamber and returned to home cages without receiving reinforcement. Responses on both levers were recorded. Antagonism testing was counterbalanced between maintenance days as in generalization testing. Test drug doses and treatment times were determined from the literature. Chlordiazepoxide (13), CGS 9896 (13) and ZK 91 296 (19) were administered 30 min, and RO 15-1788 15 min (32), prior to discrimination testing.

Measurements and Statistics

The number of training sessions (both FG 7142 and vehicle) required to achieve discriminative control (80% criterion performance) is expressed as a sessions-to-criterion (STC) measurement (23). The first STC (STC 1) indicates the number of training sessions required for an animal to reach the first training session in which 8 out of 10 consecutive sessions were injection-appropriate. The second STC (STC 2) indicates the number of training sessions required to reach the beginning of a second block in which 8 out of 10 consecutive sessions were injection-appropriate.

As described above, maintenance discrimination sessions were interspersed during generalization and antagonism testing. If, at any time during testing, an animal's maintenance discrimination fell below the 80% criterion, the animal's data were dropped from the experiments until discriminative performance returned to criterion.

The data collected in the drug discrimination sessions is expressed as both quantal and quantitative measurements, each measurement provides an indication of lever preference prior to any reinforcement. The quantal measurement is the percentage of rats selecting the FG 7142 lever as their selected lever, i.e., the first lever pressed 10 times. The quantitative measurement is the number of responses on the FG 7142 lever divided by the total number of responses on the FG 7142 and vehicle levers at the time that the tenth response is made on either lever. This fraction is expressed as a percentage. Unlike the (all-or-none) quantal measurement, the quantitative measurement accounts for responses on both the selected and unselected levers and, thus, provides a measure of the magnitude as well as direction of lever preference. Additionally, parametric statistics may be performed on the quantitative data. The advantages of using both types of measurements are more fully discussed by Stolerman and D'Mello (33).

A test compound was considered to generalize to the training drug if quantal responding following its administration was equal to or greater than 80% on the drug lever. This criterion was based on the performance level set for establishing initial acquisition of the FG 7142 cue, i.e., 80% or greater quantal responding on the FG 7142-appropriate lever. The standard deviations (SD) for the quantitative measurements reflect the variability between the two counterbalanced test sessions.

For antagonism testing, each dose of antagonist was tested twice in each rat, once following a vehicle maintenance day and once following an FG 7142 maintenance day. For each rat the individual quantitative scores from the two antagonism test sessions were averaged. Likewise, the individual quantitative scores from the FG 7142 maintenance sessions were averaged. The av-

eraged individual quantitative scores from the antagonism test sessions and FG 7142 maintenance sessions were then tested for differences between group means. Data in which more than one dose of antagonist was used was subjected to a repeated measures ANOVA followed by a post hoc Scheffé test to determine significant differences between treatment means, $p<0.05$. If only one dose of antagonist was used, the data was subjected to a one-tailed, paired t-test, $p<0.05$.

Drugs

Drugs were obtained from the following sources: FG 7142 (N'-methyl-β-carboline-3-carboxamide) and ZK 91 296 (Schering AG, Berlin); chlordiazepoxide and pentylenetetrazole (Sigma Chemical Company, St. Louis, MO); DMCM (methyl 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate) (Research Biochemicals Incorporated, Natick, MA); RO 15-1788 (Hoffmann-La Roche, Nutley, NJ); CGS 9896 (CIBA-GEIGY, Summit, NJ); norfenfluramine (A.H. Robins Research Laboratories, Richmond, VA). FG 7142, DMCM, ZK 91 296, CGS 9896, chlordiazepoxide and RO 15-1788 were suspended in a 2% Tween 80 solution (Sigma Chemical Co., St. Louis, MO) by sonication. Other drugs were dissolved in distilled water.

RESULTS

Discrimination Training and FG 7142 Dose-Response Experiments

The sessions-to-criterion and the FG 7142 dose-response data for the previously trained group has been reported (14). For the group of rats trained to discriminate FG 7142 in the present experiment, 120 training sessions were required for all animals to reach discriminative criterion. The STC 1(± SD) and STC 2(± SD) for Group 2 were 43.0(16.6) and 58.8(18.2), respectively. The quantal and quantitative dose-response data for this group are presented in Table 1. Administration of 1.25, 2.5, 5.0 and 10.0 mg/kg FG 7142 in this group resulted in quantal measurements of 16.7, 61.1, 88.9 and 92.9% and quantitative responding (± SD) 25.5(6.4), 58.0(40.0), 78.7(4.5) and 83.2(7.6), respectively.

Generalization and Antagonism Testing

Results of generalization testing with DMCM, PTZ and norfenfluramine are also presented in Table 1. Administration of 0.15, 0.23 and 0.30 mg/kg of DMCM produced quantal responding of 14.3, 28.6 and 92.9% and quantitative responding (± SD) of 27.6(4.1), 34.7(26.9) and 79.0(6.4)%, respectively. Administration of PTZ (15.0 mg/kg) to FG 7142-trained rats produced quantal and quantitative (± SD) responding of 81.3 and 70.5(4.9)%, respectively. No seizures were observed following administration of PTZ and to avoid potential seizures only one dose of PTZ was tested. In contrast to DMCM and PTZ, norfenfluramine failed to generalize to the FG 7142 discriminative stimulus. Administration of 0.7, 1.0 and 1.4 mg/kg of norfenfluramine produced quantal responding of 42.9, 57.1 and 57.1% and quantitative responding (± SD) of 41.9(6.1), 53.4(11.7) and 56.2(1.9), respectively. Testing at doses of norfenfluramine higher than 1.4 mg/kg was precluded by behavioral disruption (nonresponding).

The results of the antagonism experiments are shown in Table 2. The FG 7142 discriminative stimulus was blocked by the benzodiazepine receptor agonist chlordiazepoxide (CDP) in a dose-responsive fashion, with doses of 5.0, 10.0 and 20.0 mg/kg CDP resulting in 91.7, 41.7 and 25.0% quantal and 76.7(8.7), 45.4(9.8) and 34.6(6.7), quantitative (± SD) responding. Quantitative responding following coadministration of 20.0 mg/kg CDP with FG 7142 was significantly different from FG 7142 alone, $p<0.05$. Coadministration of the benzodiazepine receptor antagonist RO 15-1788 (3.5–20.0 mg/kg) significantly antagonized the FG 7142 discriminative stimulus only at a dose of 5.0 mg/kg. This antagonism was not dose-responsive as higher doses of RO 15-1788 (6.5–20.0 mg/kg) failed to significantly antagonize the FG 7142 cue. The benzodiazepine receptor mixed agonist/antagonist CGS 9896 also antagonized the FG 7142 discriminative stimulus, $p<0.05$. Coadministration of 30.0 mg/kg CGS 9896 with FG 7142 (5.0 mg/kg) produced quantal and quantitative responding of 8.3% and 19.8(7.8)%, respectively. Likewise, antagonism of the FG 7142 cue was observed with the benzodiazepine receptor partial agonist ZK 91 296 (15.0 mg/kg) which, when coadministrated with FG 7142, resulted in quantal responding of 27.8% and quantitative responding of 26.7(7.2)%, which was significantly different from FG 7124 (5.0 mg/kg) when given alone, $p<0.05$. Only one dose each of CGS 9896 and ZK 91 296 were employed due to a limited supply of these compounds.

TABLE 1

GENERALIZATION TO VARIOUS DOSES OF FG 7142 AND NOVEL DRUGS IN RATS TRAINED TO DISCRIMINATE 5.0 mg/kg FG 7142 FROM ITS VEHICLE

Treatment	Dose (mg/kg)	% Responding on the FG 7142 Lever: Quantal	Quantitative (± SD)	N
Vehicle	—	0.0	11.2 (5.6)	9
FG 7142	1.25	16.7	25.5 (6.4)	9
	2.5	61.1	58.0 (40.0)	9
	5.0	88.9	78.7 (4.5)	9
	10.0	92.9	83.2 (7.6)	7
DMCM	0.15	14.3	27.6 (4.1)	7
	0.23	28.6	34.7 (26.9)	7
	0.30	92.9	79.0 (6.4)	7
PTZ	15.0	81.3	70.5 (4.9)	8
NF*	0.7	42.9	41.9 (6.1)	7
	1.0	57.1	53.4 (11.7)	7
	1.4	57.1	56.2 (1.9)	7

*Norfenfluramine.

DISCUSSION

The present study demonstrates a second successful investigation in which rats were trained to discriminate the interoceptive cue of FG 7142, a drug previously reported to be incapable of controlling discriminative stimulus responding (20). The first successful training of rats to discriminate FG 7142 employed an initial training dose of 2.5 mg/kg FG 7142, which was subsequently increased to 5.0 mg/kg after 95 training sessions in an effort to stabilize the discriminative performance of the group (14). As a lengthy training period was required to establish the FG 7142 discrimination in these rats, a higher dose of FG 7142 (5.0 mg/kg) was chosen as the training dose for the group of rats trained to discriminate FG 7142 in the present study. This higher dose did not, however, facilitate acquisition of the FG 7142 discriminative stimulus. At this higher training dose no seizures were observed.

TABLE 2

ANTAGONISM OF THE FG 7142 DISCRIMINATIVE STIMULUS BY BENZODIAZEPINE RECEPTOR LIGANDS

Treatment	Dose (mg/kg)	% Responding on the FG 7142 Lever: Quantal	Quantitative (±SEM)	N
FG 7142	5.0	93.8	78.8 (7.3)	6
FG 7142 + CDP†	5.0	91.7	76.7 (8.7)	6
	10.0	41.7	45.4 (9.8)	6
	20.0	25.0	34.6 (6.7)*	6
FG 7142	5.0	93.8	78.8 (7.3)	6
FG 7142 + RO 15-1788	5.0			
	3.5	33.3	31.8 (13.1)	6
	5.0	8.3	11.6 (5.2)*	6
	6.5	66.7	62.1 (9.8)	6
	10.0	41.6	43.4 (14.8)	6
	20.0	83.3	73.3 (9.8)	6
FG 7142	5.0	100.0	81.3 (6.0)	6
FG 7142 + CGS 9896	5.0			
	30.0	8.3	19.8 (7.8)*	6
FG 7142	5.0	92.6	83.0 (2.7)	9
FG 7142 + ZK 91 296	5.0			
	15.0	27.8	26.7 (7.2)*	9

*Significantly different from quantitative measurement when FG 7142 was administered alone, $p<0.05$.

†Chlordiazepoxide.

The present results indicate that FG 7142 produces a discriminative stimulus based on its inverse agonist properties as evidenced by the generalization of FG 7142 to the inverse agonist DMCM and the ability of chlordiazepoxide, CGS 9896, ZK 91 296 and RO 15-1788 to antagonize the FG 7142 discriminative stimulus. The dose-responsive generalization of FG 7142 to the inverse agonist DMCM is consistent with the results of Nielsen et al., who reported that FG 7142 (10.0 mg/kg) produced DMCM-appropriate responding in rats trained to discriminate DMCM (20). Together, these studies establish the existence of a symmetrical generalization between DMCM and FG 7142.

In the discriminative stimulus paradigm, FG 7142 antagonizes the chlordiazepoxide discriminative stimulus in rats trained to discriminate 5.0 mg/kg of chlordiazepoxide (31,32). In the present study, chlordiazepoxide (5.0–20.0 mg/kg) produced a dose-responsive antagonism of the FG 7142 discriminative stimulus (Table 2). This antagonism was, however, observed only at a dose of chlordiazepoxide (20.0 mg/kg) which produced behavioral disruption, i.e., depressed responding rate. The ability of benzodiazepines to antagonize the discriminative stimulus effects of other inverse agonists has been previously reported. The benzodiazepines diazepam (1.25 mg/kg) and midazolam (0.32 mg/kg) are effective antagonists of discriminative behavior trained by low dose DMCM (0.2 mg/kg) (19) and β-CCE (1.0 mg/kg) (35), respectively, whereas diazepam (2.5 mg/kg) was ineffective in antagonizing high dose DMCM discriminations (0.4–0.7 mg/kg) despite its ability to dramatically depress responding (19). As suggested by Nielsen et al. (19), the inability of diazepam to antagonize high doses of DMCM may be related to the disruptive effects of this drug at high doses that may preclude testing at doses sufficient to produce antagonism. In light of the behavioral disruption, i.e., delayed onset of lever pressing or, in some cases, nonresponding, noted with full agonist benzodiazepines in the present study as well as in the study cited above, these compounds may not be the most appropriate agents with which to antagonize inverse agonist discriminative stimuli.

Recently, a variety of nonsedating, anxiolytic benzodiazepine receptor agonists have been synthesized. These compounds produce anxiolysis without the sedation and muscle relaxation associated with the classical benzodiazepines and, thus, may antagonize inverse agonist discriminative stimuli without producing behavioral disruption. In the present study the partial agonist ZK 91 296 (24,26) and mixed agonist/antagonist CGS 9896 (1, 2, 6) antagonized the FG 7142 discriminative stimulus without suppressing discriminative responding. The ability of ZK 91 296 to antagonize an inverse agonist discriminative stimuli without interfering with responding has been previously demonstrated in rats trained to discriminate high doses of DMCM (19). Therefore, based on the efficacy of ZK 91 296 and CGS 9896 in antagonizing the FG 7142 discriminative stimulus, and the lack of behavioral disruption associated with their use, it appears that partial agonists or mixed agonist/antagonists may be used more advantageously than full agonists to antagonize inverse agonist discriminative stimuli.

The benzodiazepine receptor antagonist RO 15-1788 also was observed to antagonize the FG 7142 discriminative stimulus. This antagonism was not, however, dose-responsive as a low dose of RO 15-1788 (5.0 mg/kg) but not higher doses of RO 15-1788 antagonized the FG 7142 cue. Similarly, in both DMCM-trained rats (19) and β-CCE-trained monkeys (35), high doses of RO 15-1788 (10.0–40.0 mg/kg) were ineffective in antagonizing the DMCM and β-CCE cues, whereas lower doses of RO 15-1788 (1.0–5.0 mg/kg) antagonized the β-CCE cue (35). Interestingly, when administered alone to β-CCE-trained monkeys, high doses of RO 15-1788 (10.0–17.8 mg/kg) substituted for the β-CCE discriminative stimulus (35). Therefore, in animals trained to discriminate inverse agonists, it appears that RO 15-1788 may act as an antagonist at low doses and as an inverse agonist at high doses. These findings are not in agreement with a number of biochemical and behavioral studies which indicate that RO 15-1788 acts as an antagonist at low doses and a partial agonist at high doses (10). The discrepancy in the efficacy of RO 15-1788 between the drug discrimination studies and other studies may be due to the chronic nature of the drug discrimination studies. Based on results obtained in animals trained to discriminate DMCM, Nielsen et al. (19) have proposed that chronic treatment with benzodiazepine receptor inverse agonists may cause a shift in the efficacy of benzodiazepine receptor ligands such that a compound which lacks intrinisic activity (an antagonist) may be converted to inverse agonist.

The present results indicate that FG 7142 produces a discriminative stimulus based on its inverse agonist properties, however, they do not indicate the behavioral nature of this cue as there are at least three benzodiazepine receptor-mediated behavioral effects of FG 7142, i.e., its anxiogenic, proconvulsant and anorectic properties. Previous results indicate that the FG 7142 cue may be anxiomimetic in nature based on the generalization of the FG 7142 cue to the physiological stressor footshock and partial generalization to novelty (14). In the present study FG 7142 was shown to generalize to PTZ, a convulsant which produces anxiety in man (27). Similarly, the PTZ cue is mimicked by FG 7142 (31). In drug discrimination studies, the interoceptive nature of the PTZ cue has been extensively characterized and it is believed

to be based on the anxiogenic rather than the convulsant properties of PTZ (12). Thus, the discriminative similarities between FG 7142 and PTZ support the idea that the cue associated with FG 7142 is based on the anxiomimetic properties of FG 7142 and not its proconvulsant action.

Although it cannot be conclusively determined that the proconvulsant action of FG 7142 does not contribute to its cueing properties, it is worth noting that the training dose used in this study is 6–8 times lower than doses used for kindling purposes (8,16). Furthermore, it is unlikely that these animals were close to seizure threshold at the FG 7142 training dose since seizures were not observed in any animal following administration of FG 7142 at twice the FG 7142 training dose and no seizures were observed in animals tested with PTZ.

In addition to possessing anxiogenic and proconvulsant properties, FG 7142 has anorectic action (4,5). To assess the involvement of the anorectic effects of FG 7142 in the FG 7142 discriminative stimulus, the anorectic agent norfenfluramine (3, 18, 29) was administered to the FG 7142-trained rats. In the discriminative stimulus paradigm norfenfluramine appears to produce a discriminative stimulus related to its anorectic properties, as food-deprived rats trained to discriminate the interoceptive effects of food-deprivation (hunger) versus nondeprivation (satiation) responded as if they were satiated following administration of 1.0 mg/kg norfenfluramine, IP (28). In FG 7142-trained rats norfenfluramine did not mimic the FG 7142 discriminative stimulus indicating that the discriminative stimulus of FG 7142 may not be related to its anorectic properties. Additionally, the lack of generalization of the FG 7142 cue to norfenfluramine in this study and to the $5HT_{1B}$ agonist mCPP (15) and dopamine receptor agonist apomorphine (personal observation) demonstrate that the FG 7142 cue is a pharmacologically specific stimulus.

In conclusion, FG 7142 produces an inverse agonist discriminative stimulus as evidenced by its generalization to DMCM and antagonism by the benzodiazepine receptor agonist chlordiazepoxide, partial agonist ZK 91 296, mixed agonist/antagonist CGS 9896 and antagonist RO 15-1788. Furthermore, consistent with our previous findings that the FG 7142 cue generalizes to a physiological stressor, the generalization of FG 7142 to PTZ suggests that the anxiogenic properties of FG 7142 may underlie the FG 7142 discriminative stimulus.

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