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Discriminative Stimulus Control by the Anxiogenic β-Carboline FG 7142: Generalization to a Physiological Stressor

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LEIDENHEIMER, N. J. AND M. D. SCHECHTER. *Discriminative stimulus control by the anxiogenic β-carboline FG 7142: Generalization to a physiological stressor.* PHARMACOL BIOCHEM BEHAV 30(2) 351–355, 1988.—Drug discrimination was employed to investigate the similarities between FG 7142-induced anxiogenesis and the stress produced by exposure to either a novel environment or to footshock. Eight rats were trained to discriminate between the stimulus properties of the β-carboline FG 7142 (5.0 mg/kg) and its vehicle in a two-lever, food motivated operant task. Once trained, decreasing doses of FG 7142 produced fewer FG 7142-appropriate responses and the dose-response relationship yielded an ED_{50} of 1.45 mg/kg. Rats were subsequently subjected to two physiological/environmental stressors, footshock and novelty, and then tested in the discriminative paradigm. Exposure to novelty resulted in partial FG 7142-appropriate responding, whereas footshock sessions produced responding predominately on the FG 7142-appropriate lever. This is the first report of stimulus control by FG 7142 and it is likely that the interoceptive cue state produced by this compound is anxiogenic in nature, as reported to occur in man. The anxiogenic nature of the FG 7142 discriminative stimulus is supported by the generalization of FG 7142 to the state produced following stressful environmental manipulation.

Drug discrimination FG 7142 β-Carbolines Novelty Rats Footshock

FG 7142 (β-carboline-3-carboxylic acid methyl amide) is a β-carboline which binds with high affinity to the benzodiazepine receptor [9]. Unlike benzodiazepines which are widely prescribed anxiolytics, FG 7142 is an intense anxiogenic in man whose effects can be reversed by benzodiazepine administration [3]. FG 7142 has also been observed to be anxiogenic in rats, in that it decreases time spent in social interaction without decreasing motor activity [6,7] and enhances shock-induced suppression of drinking in the Vogel test [1,16], behaviors commonly associated with anxiety.

In the discriminative stimulus (D.S.) paradigm, rats trained to discriminate pentylenetetrazole (PTZ) from saline respond predominantly on the PTZ-appropriate lever following FG 7142 administration [19]. Furthermore, FG 7142 produces discriminative stimulus effects similar to the inverse agonist methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM) in rats trained to discriminate DMCM from vehicle [11]. Despite the activity of FG 7142 as the novel test drug in these rats trained to discriminate other drugs in the D.S. paradigm, one previously reported attempt to establish discriminative stimulus control with FG 7142 was unsuccessful [12]. The purpose of the present experiment was to attempt to train rats to discriminate the D.S. properties of the anxiogenic β-carboline FG 7142 and, if successful, to attempt a generalization of a drug-induced state to the state produced by physiologically/environmentally-induced stress.

METHOD

Subjects

Eight experimentally-naive male Sprague-Dawley rats (Zivic Miller, Allison Park, PA), weighing between 190–235 g at the beginning of the experiment, were individually housed and maintained on a 12 hour light (0600–1800)/12 hour dark cycle in a room kept at temperatures between 20–22°C. They received water ad lib and a daily rationing of commercial rat chow to maintain 80–85% of their free-feeding weights.

Apparatus

Eight standard rodent operant chambers (Lafayette Instruments Corp., Lafayette, IN) were used as the experimental space. Each chamber contained two levers situated 7 cm apart and 7 cm above a metal 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

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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.

A modified operant chamber, with both levers removed and the food delivery hole blocked by a metal plate, served as a shockbox. The grid floor of this box was identical to those used in the operant chamber and consisted of 18 metal bars spaced 1 cm apart. A scrambled current was delivered through the grid floor by an A615C Master Shocker (Lafayette Instruments Company, Lafayette, IN). To control the duration and frequency of the shocks, a Grass SD9 Stimulator (Grass Instruments, Quincy, MA) was employed to trigger the Master Shocker. Unlike the discrimination chamber, the shockbox was not enclosed in an unlit sound-attenuated cubicle but was placed in a well-lit laboratory adjacent to the laboratory used for discrimination training/testing.

Lever Response Training Procedure

Prior to discrimination training, food-deprived rats were trained (shaped) to press the levers in the operant chamber for food reinforcement (45 mg Noyes pellets). Training sessions were held once a day, 5 days a week. At the start of the experiment, one lever in each chamber was designated as the "vehicle lever." The vehicle lever for half the group (n=4) was that lever located to the right of the food receptacle. For the remaining rats the left lever served as the vehicle lever. This pattern of lever assignment controlled for any possible left/right lever preference. Thirty min prior to the training session rats were administered 1 ml/kg of vehicle and were rewarded solely for responses on their designated vehicle lever. Initially rats were trained to respond on the vehicle lever on a fixed ratio (FR) schedule of one, i.e., one response resulted in one reinforcement. Over seven training sessions the FR schedule was gradually increased to an FR 10, i.e., ten responses yielded one reinforcement. Animals were removed from the chamber and returned to home cages after receiving 40 reinforcements.

Once an FR 10 was established on the vehicle lever, training began on the opposite lever, the "FG lever," following FG 7142 administration.Thirty min following the administration of an equal volume of FG 7142 (2.5 mg/kg) rats were rewarded for responses on the FG lever only. As with vehicle administration, the initial schedule of an FR 1 was gradually increased to an FR 10 over a period of five days.

Discrimination Training

Once FR 10 responding was established on both levers, discrimination training began. Thirty min prior to daily discrimination training sessions, rats received either 1 ml/kg of vehicle (V) or vehicle containing 2.5 mg/ml FG 7142 (FG) according to the following two week pseudo-random injection schedule: FG,V,V,FG,FG; V,FG,FG,V,V. At the beginning of each session the first lever upon which ten responses were made was considered the selected lever for that session. At the time of the tenth response, presses on both the selected and unselected levers were each recorded. Whether the selected lever was correct or incorrect for the injection received, the session was continued until 400 responses were made on the correct lever and, therefore, 40 reinforcements were received. As during lever response training, responses on the FG lever were rewarded only following FG 7142 administration and responses on the vehicle lever were rewarded only following vehicle injections. Responding on the inappropriate lever was inconsequential. As discussed in the Results section, the initial training dose of 2.5 mg/kg FG 7142 was increased to 5.0 mg/kg on the 96th discrimination training session where it remained throughout the experiment.

The two-week psuedo-random injection schedule was repeated until the selected lever was correct for the injection received in 8 out of 10 consecutive training sessions. Animals were required to achieve this level of performance twice before testing commenced. The number of training sessions required to achieve this criterion is expressed as a sessions-to-criterion (STC) measurement [13]. The first STC (STC 1) indicates the number of sessions required to reach the first session in the first series of 8 out of 10 correct consecutive sessions. The first session in the second series of 8 out of 10 correct selections constitutes the STC 2. Data collection began when all animals had fulfilled this 80% criterion.

Dose-Response Testing

Once discriminative criterion was attained, the discrimination training regimen was limited to every other day to maintain discrimination. On intervening days, rats were tested with varying doses of FG 7142 so that each dose was tested twice, once following a drug maintenance session and once following a vehicle maintenance session. This counterbalancing was used to control for any possible residual influence from the previous maintenance session. If, at any time during testing, an animal's maintenance discrimination fell below the 80% criterion, the animal's data were dropped from the experiment. This occurred in one animal during dose-response testing.

In the FG 7142 dose-response sessions animals were injected prior to the discrimination session with doses of FG 7142 different from that used in maintenance, i.e., either 2.5 or 1.25 mg/kg. Thirty min post-injection the rats were placed into the discrimination chamber and were immediately removed, without receiving reinforcement, following the tenth response on either lever. At this time presses on both the drug and vehicle levers were recorded and used to calculate the quantitative measurement (see Measurements and Statistics).

Initial Exposure and Habituation to the Novelty of the Shockbox

As in dose-response testing, novelty and habituation test sessions were interspersed between maintenance sessions to ensure that discrimination was maintained at the 80% reliability criterion. On test session days rats were injected with vehicle, immediately placed into the shockbox for 20 min *without* being shocked, removed and immediately placed into the operant chamber. After making ten responses on either lever, the rats were removed without receiving reinforcement, and returned to their home cages. The non-shock test sessions were continued until responding was vehicle-like. The first non-shock session was designated as the novel environment measurement (see the Results section). Additional non-shock sessions served to habituate the rats to the novelty of the shockbox prior to the footshock session.

Footshock Experiment

Following habituation to the novelty of the shockbox,

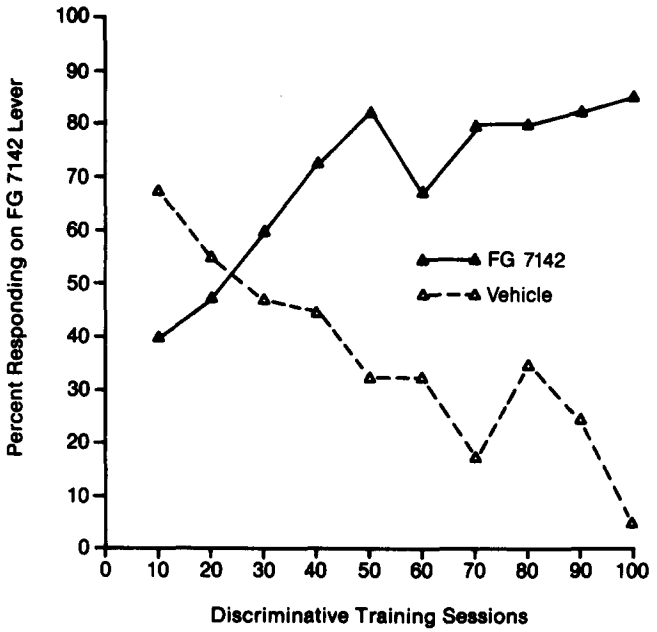

FIG. 1. Acquisition curve of rats (n=8) trained to discriminate FG 7142 from its vehicle. Ordinate: Percent of rats choosing the FG 7142 lever first; Abscissa: Discriminative training sessions as detailed in the Method section.

rats were tested in the drug discrimination chamber after receiving a mild footshock. Rats were injected with vehicle, placed into the shockbox and subjected to a scrambled footshock (0.2 mA, 160 msec duration with a 330 msec interval) for 20 min. They were immediately placed in the discrimination chamber and promptly removed, without receiving reinforcement after making ten selections on either of the two levers.

Measurements and Statistics

The data collected in the drug discrimination sessions is expressed as both quantal and quantitative measurements and each measurement provides an indication of lever preference prior to any reinforcement. The quantal measurement is the percentage of rats selecting the drug lever as their selected lever, i.e., the lever pressed 10 times first. The quantitative measurement is the number of responses on the drug lever divided by the total number of responses on both the drug and vehicle lever 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, thus providing a relative measure of the magnitude as well as direction of lever preference. Additionally, 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 [20].

The Litchfield-Wilcoxon procedure [10], which employs probit vs. log dose effects, was used to generate an ED_{50} from the FG 7142 quantal dose-response data. Quantitative dose-response measurements (Table 1) represent the average (±SD) of the individual session quantitative means for each

TABLE 1

EFFECT OF VARIOUS DOSES OF FG 7142 ON RATS (n=7) MAINTAINED TO DISCRIMINATE 5.0 mg/kg FG 7142 FROM ITS VEHICLE

Treatment	Dose (mg/kg)	Quantal Responding	Quantitative Responding (S.D.)
Vehicle	—	7.1	15.7 (16.3)
FG 7142	5.0	100.0	78.7 (2.5)
	2.5	78.6	67.2 (13.5)
	1.25	42.9	49.3 (5.7)
ED50 (mg/kg)		1.45	1.27
95% confidence limits		(0.96–2.18)	(0.47–3.46)

treatment. Quantitative data (Table 2) following FG 7142 and vehicle sessions, as well as novel environment and footshock, were subjected to a repeated measures analysis of variance followed by a post hoc Scheffé test to determine significant differences between treatment means ($p<0.05$). The quantitative data used as FG 7142 and vehicle treatment values were collected from FG 7142 and vehicle maintenance days as they were interspersed during the period of physiological/environmental manipulations. During this period, quantitative measurements reflect the average (±SD) of quantitative scores derived for each animal. This was necessary since habituation to stress precluded counterbalancing.

Treatments

FG 7142 (Research Biochemicals Incorporated, Wayland, MA) was suspended in a 2% solution of Tween 80 (Sigma Chemical Company, St. Louis, MO) by sonification and administered in a volume of 1 ml/kg, IP. The 2% solution of Tween 80 (1 ml/kg, IP) was used for vehicle injections.

RESULTS

Discrimination Training Sessions

Initial training began at a 2.5 mg/kg dose of FG 7142 (see the Method section). After 95 training sessions, the animals as a group had not achieved stable discriminative performance (Fig. 1). Although 7 of 8 animals had reached the 80% criterion for discrimination at this time, the discriminative stimulus cue appeared to be fragile in nature as some animals were unable to maintain this 80% criterion over a continued period of time. To bring the remaining animal to criterion, and to stabilize the discriminative performance of the group, the training dose was increased to 5.0 mg/kg for all subjects on the 96th training session. Following this increase in the FG 7142 training dose, discriminative criterion was rapidly achieved and maintained. The 5.0 mg/kg dose was continued for all animals for the remainder of the experiment. For the eight animals, the STC 1 and STC 2 were 30.6 (± 14.0) and 54.6 (± 21.1), respectively.

Dose-Response Relationship

The result of experiments in which various doses of FG 7142 were tested is presented in Table 1. Doses of 1.25, 2.5 and 5.0 mg/kg FG 7142 produced quantal responding of 42.9, 78.6 and 100%, respectively. Analysis of this dose-response

TABLE 2

DISCRIMINATIVE RESPONDING FOLLOWING EXPOSURE TO NOVEL AND STRESSFUL STIMULI

Treatment	Quantal Responding	Quantitative Responding (S.D.)
Vehicle	8.3	19.0 (10.3)
FG 7142 (5.0 mg/kg)	100.0	94.0 (10.4)
Novel Environment	62.5	65.3 (24.7)*
Footshock (0.2 mA)	87.5	73.2 (25.3)†

*Significantly different from both FG 7142 and vehicle quantitative measurement ($p<0.05$).

†Significantly different from vehicle quantitative measurement ($p<0.05$).

curve [10] yielded an ED_{50} (95% of confidence interval) of 1.45 (0.96–2.18) mg/kg for the quantal measurements and a similar ED_{50}=1.27 (0.47–3.46) mg/kg for the quantitative measurements.

Exposure to Novelty and Footshock

Initial ("novel") exposure to the modified operant chamber (see the Method section) produced quantal responding of 62.5% (Table 2). Quantitative responding of 65.3 (±24.7) was significantly different from both the FG 7142 and vehicle maintenance sessions ($p<0.05$) as shown in Table 2. Following the first exposure to the modified operant chamber each rat was subjected to three non-shock habituation sessions. Sessions one through three produced quantitative responding of 41.6 (±37.0), 38.7 (±30.8) and 27.7 (±28.4). Although the first habituation sessions produced responding which was not significantly different ($p<0.05$) from quantitative responding of interspersed vehicle administration, habituation sessions were continued until responding became less variable (as indicated by decreased standard deviation) and more vehicle-like.

Following the one footshock session, 87.5% of the rats selected the FG-appropriate lever. As shown in Table 2 quantitative responding of 73.2 (±25.3) was not significantly different from the quantitative measure of interspersed FG 7142 sessions.

DISCUSSION

Although FG 7142 has been reported to produce a discriminative stimulus that is similar to the drug used for training in both PTZ-trained [19] and DMCM-trained [11] rats, it has never been reported to be capable of serving as the training drug in a D.S. paradigm; one previous attempt in another laboratory to establish discriminative stimulus control in over 50 training sessions with FG 7142 (5–30 mg/kg) was unsuccessful [12]. The present report indicates that FG 7142 (5.0 mg/kg) can adequately control discriminative responding in the rat when administered 30 min prior to the discrimination session. An average of 54.6 (±21.1) sessions were required to reach the 80 percent appropriate responding criterion. Differences in training dose could account for these disparate results since the dose range of discrimination for some drugs may be quite narrow. Furthermore, FG 7142 may require an extended training period to achieve reliable discriminative stimulus control and, indeed, 2.5 mg/kg FG 7142 produced only unstable discriminative performance. Raising the training dose to 5.0 mg/kg, however, during the last session block ensured stability.

The initial training dose of 2.5 mg/kg was selected to avoid the seizure kindling effects reported following chronic FG 7142 treatment at much higher doses (15 mg/kg twice daily, for ten days [2]). After 95 sessions of FG 7142 training at 2.5 mg/kg, no seizure activity was observed. Upon increasing the training dose to 5.0 mg/kg, seizures were consistently observed in one rat. However, the 1.25 and 2.5 mg/kg doses of FG 7142 administered to this one rat during dose-response testing did not produce convulsions. Despite continued, but mild, seizures upon receiving maintenance doses of FG 7142 (5.0 mg/kg), nearly 100% discrimination was maintained by this animal. The possibility that this rat may cue to the exteroceptive state of the seizure seems unlikely since he was subsequently observed to generalize to footshock and a test drug (unpublished) which does not produce convulsions.

In this experiment, FG 7142 was selected as the training drug due to its reported anxiogenic activity in both man [3] and rodent [1, 6, 7, 15]. Another laboratory has used the drug discrimination paradigm to train rats to discriminate the stimulus effects of another inverse agonist DMCM. These investigators reported the need to individualize doses of DMCM over a wide range (0.4–0.7 mg/kg) to avoid seizure activity when using DMCM for D.S. control. FG 7142 (5.0 mg/kg) provides an extremely stable stimulus cue as evidenced in maintenance sessions and, in contrast to DMCM, FG 7142 appears to be less likely to induce seizures. This is further evidenced by the reported observation that following a 6–10 day pause in the DMCM experiment cited above, a supersensitivity developed that resulted in lethal convulsions upon readministration of DMCM [11]. In the present experiment, no lethality was observed following a 3-week pause in experimentation. It is, thus, likely that the apparent liabilities of FG 7142 training, i.e., a lengthy training period and possible seizure kindling effects may both be overcome by employing a training dose greater than 2.5 mg/kg to facilitate training but less than 5.0 mg/kg to minimize any seizure activity.

This study demonstrates that exposure to stressful manipulations such as a novel environment or mild footshock can produce a state similar to the interoceptive cue produced by FG 7142. In the rat, exposure to a novel environment has been well established as a stressor [4,5]. An elevation in plasma corticosterone has long been regarded as an indicator of this stress. Interestingly, the increase in corticosterone levels following exposure to this stressor can be blocked by pretreatment with benzodiazepines, suggesting a relationship between the benzodiazepine receptor and this type of stress [4,5]. Furthermore, Pellow [14] has shown that FG 7142 not only increases rat basal corticosterone levels itself, but that it also potentiates the increase in corticosterone levels seen following exposure to novel environment. Behaviorally the level of exploratory activity in unfamiliar surroundings is considered to reflect anxiety levels. When pretreated with benzodiazepines, rats exposed to a novel environment show an increase in exploratory behavior whereas pretreatment with an inverse agonist, such as FG 7142, decreases exploratory activity [15].

To assess the nature of stress produced by novelty, rats were briefly exposed to a novel environment and immediately placed into the discrimination chamber. The partial transfer of the FG 7142 interoceptive cue to this noninvasive stressor may reflect the anxiogenic nature of novelty. The subtlety of this stressor may account for the incompleteness of the FG 7142 generalization since the FG 7142 cue may represent a more intense internal state. Repeated exposure of rats to the novel environment produced progressively fewer responses on the FG 7142 lever, suggesting an habituation to the environment. Habituation to novelty has previously been reported by Pfister [17] and File [4] who have shown that the plasma corticosterone response to novelty wanes upon repeated exposure.

Although novelty was perceived as being only partially FG 7142-like, mild footshock produced complete generalization to FG 7142. Footshock has been shown to be moderately stressful in rodents as evidenced by an activated pituitary-adrenal axis [8]. In addition, this stress is accompanied by changes in several neurotransmitter systems, particularly the medial prefrontal (MPF) cortical dopamine system. An increase in MPF dopamine levels following footshock has been established [18]. Recently, Tam and Roth have shown a selective activation of this system following FG 7142 administration [21]. Both footshock and FG 7142 induced increases in MPF dopamine may be blocked by pretreatment with benzodiazepines [18,21]. The present results provide behavioral evidence for the similarities between FG 7142 and the external stressor footshock.

In conclusion, the FG 7142 discriminative stimulus may provide a useful tool for investigating the anxiogenic nature of stressful behavioral manipulations. Future studies employing other anxiogenic drugs, such as DMCM and PTZ, are needed to further establish the nature of the FG 7142 cue.

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