Pharmacology Biochemistry and Behavior, Vol. 43, pp. 1195–1200, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Chlordiazepoxide Reduces the Generalised Anxiety, But Not the Direct Responses, of Rats Exposed to Cat Odor

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Received 16 June 1992

ZANGROSSI, H., JR., AND S. E. FILE. *Chlordiazepoxide reduces the generalised anxiety, but not the direct responses, of rats exposed to cat odor.* PHARMACOL BIOCHEM BEHAV **43**(4) 1195–1200, 1992.—Rats were treated for 5 days with vehicle or chlordiazepoxide (CDP, 5, 10, or 20 mg/kg/day) and then exposed to a cloth impregnated with a neutral or cat odor. Those exposed to cat odor made significantly fewer contacts with the cloth and spent less time in contact with it and more time sheltering than those exposed to the neutral odor. CDP (5 mg/kg) significantly increased the time in contact with both odor cloths, but there were no other significant effects in the cat odor group. Rats previously exposed to cat odor showed significant anxiogenic responses in the social interaction and elevated plus-maze tests that were significantly reversed by CDP. There was no reduction in the responses to the cat odor on a second occasion as a result of the first exposure occurring after treatment with CDP (5 or 20 mg/kg). The anxiogenic effects of pentylenetetrazole (20 mg/kg) as detected in the social interaction and plus-maze tests were unaffected by prior odor experience. It is suggested that during exposure to the cat odor the responses of rats reflect avoidance components of a phobic anxiety state. Benzodiazepines are relatively ineffective against these responses in contrast to their efficacy against the generalised anxiety responses detected in the social interaction and plus-maze tests.

Anxiety Phobia Benzodiazepines Cat odor

THE Blanchards' group (1,2) have described the pattern of behavioral responses of rats to the actual presence, or to the odor, of a predator. They proposed that behaviors exhibited in the presence of a predator reflected a fear response, whereas behaviors evoked by cat odor reflected anxiety. In a previous study in this laboratory (11), it was shown that exposure to cat odor produced consistent behavioral responses in laboratory rats during the actual presentation of the odor. The consequences of cat odor exposure were also generalised to, and detected in, two tests of anxiety: the social interaction and plus-maze tests. It has been proposed that the behaviors observed during cat odor exposure may reflect a phobic anxiety state, whereas the changes subsequently observed in the plus-maze and social interaction tests reflect a generalised state of anxiety.

In Experiment 1, the effects of a benzodiazepine [chlordiazepoxide (CDP)] were examined during cat odor exposure as well as on the subsequent behavioral consequences as measured in the social interaction and plus-maze tests. The benzodiazepines have been shown to be ineffective or of low efficacy in the treatment of human phobias (7). We hypothesised that if the behavioral responses observed during odor exposure reflected a state of phobic anxiety then CDP should have a mild or no effect on these responses. On the other hand, a positive action would be expected on the generalised effects detected in the social interaction and plus-maze tests.

In Experiment 2, we investigated whether exposure to a phobic object (cat odor) while treated with CDP had any effects on the behavior during a subsequent exposure to cat odor. Animals injected with the low (5 mg/kg) and high (20 mg/kg) doses of the drug in Experiment 1 were reexposed, undrugged, to cat odor 3 days later.

Experiment 2 also provided a further test of whether the state engendered by cat odor was distinct from other anxiety states. Pentylenetetrazole (PTZ) acts at a binding site associated with the chloride channel on the GABA–benzodiazepine receptor complex and has anxiogenic actions in man (10) and in the social interaction and elevated plus-maze tests (5,9). We hypothesised that if the state evoked by PTZ resembled that evoked by cat odor it would serve as a reminder of that phobic state and therefore have a greater effect in rats previously exposed to cat odor than in those exposed to neutral odor. Alternatively, if the two anxiety states were distinct then PTZ would be expected to have the same effect in both groups.

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METHOD

Animals

Male hooded Lister rats (Olac Ltd., Bicester, UK) weighing approximately 250 g were housed with food and water freely available in a room maintained at 22°C with lights on from 0700–1900 h. Rats were housed in groups of five until 5 days before testing, when they were singly housed.

Apparatus

Animals were exposed to neutral and cat odor cloths while remaining in their home cages but in a separate room from where they were normally housed. The cage was a Perspex box 40 × 24 cm covered by a raised wire top. The height between the cage floor and wire top was 19 cm. Food and water compartments were localized at one end of the cage and extended 12 cm. During the experiment, these compartments retained their usual water bottle and food. The behavior of rats was videorecorded to be scored at a later date.

Cat odor was obtained by rubbing a damp cloth vigorously against the fur of a laboratory-housed domestic cat for 5 min. This procedure was carried out 1 h before the experimental session. The cat odor cloth was kept in a sealed plastic bag. Each cloth was used for four exposures only. Damp pieces from the same original cloth were used for the neutral odor.

The social interaction test arena was a wooden box 60 × 60 cm, with 35-cm-high walls lit by dim light (35 radiometric lux). The social activity of animals in the arena was recorded on videotape. Infrared photocells were mounted in the walls 4.5 and 12.5 cm from the floor and interruption of these beams provided automated measures of locomotor activity and rearing, respectively. The output from the photocells was entered into a microcomputer.

The elevated plus-maze was made of wood, with two opposite open arms, 50 × 10 cm, and two opposite enclosed arms of the same size but with walls 40 cm high. The arms were connected by a central square and thus the maze formed a plus-sign. It was elevated 50 cm above the floor. Rats were observed on a TV monitor in an adjacent room by an observer with no knowledge of rats' treatment. The number of entries onto, and time spent on, open and enclosed arms were scored using a keyboard entry into an IBM PC. An entry was defined as both forepaws in the respective arm.

The holeboard was a wooden box 60 × 60 × 35 cm with four holes equally spaced in the floor, each 3.8 cm in diameter. Infrared cells 4.5 cm from the floor of the box provided automated measures of locomotor activity.

Drugs

CDP HCl (Roche Products Ltd., Welwyn Garden City) and PTZ (Sigma Chemical Co., Poole) were dissolved in distilled water. All drugs were given IP in an injection volume of 2 ml/kg 30 min before testing. Control rats received equivolume injections of distilled water.

Statistics

In Experiment 1 the responses during the odor exposures were analysed by two-way analyses of variance (ANOVAs) with odor and drug treatment as independent factors. The data from the social interaction and plus-maze tests were analysed by one-way ANOVAs. Duncan's tests were used for comparisons of individual groups following ANOVA. The data from Experiment 2a were analysed by split-plot ANOVA with drug treatment as the independent factor and trials as the repeated measure. The data from Experiment 2b were analysed by a two-way ANOVA with odor and drug treatment as independent factors.

PROCEDURE

Experiment 1

Cat odor exposure. One hundred and 18 rats were randomly allocated among the control (distilled water) and CDP (5, 10, and 20 mg/kg) groups and then to the neutral and cat odor conditions (n = 12–16 rats in each drug treatment and odor group). To minimise the sedative effects of CDP, daily injections were given for 5 days prior to any odor exposure. Control groups received 5 days of distilled water injections. All odor exposures took place in a separate small, dimly lit room and neutral exposures always preceded cat odor exposures to prevent any traces of cat odor influencing the neutral odor group. Before the first cat odor exposure, an impregnated cloth was left in the test room for 10 min. Immediately before odor exposure, two rats were carried to the exposure room, each in its own home cage. The cages were placed side by side and the odor cloth wedged between the cage tops at the opposite end from the food and water containers. The odor exposure was 5 min and rats were videotaped for later scoring. A cloth contact was defined as a direct contact or sniffing ≤5 cm from the cloth; sheltering was defined when the rat was underneath the food and water compartments.

After exposure, rats were returned to the animal house and 30 min later tested in the social interaction test, which took place in a separate room from the odor exposure.

Social interaction. All animals that were exposed to cat odor and the control group exposed to neutral odor were tested in the social interaction test. Two days prior to the social interaction test, rats had been allocated to test partners from the same chronic treatment (the difference in weight being not more than 5 g), and on each day they were familiarised with the test arena for 4.5 min. This took place undrugged, immediately before each rat's daily injection. Thus, the social interaction test took place under the low-light, familiar test condition that generates maximal scores in control animals and is hence most sensitive to anxiogenic effects.

The social interaction test lasted 4.5 min and an observer, blind to the drug treatment of rats, scored for each pair the time spent in active social interaction.

Plus-maze. Immediately after the social interaction test, one animal of each pair exposed to cat odor was tested in the plus-maze except the group CAT–10 mg/kg, in which both animals from the last two pairs were scored (to make up equal group numbers of eight animals). Each rat was placed in the central square of the plus-maze and allowed 5 min of free exploration. The plus-maze was in a different room from the odor exposure and social interaction test.

Holeboard. The rats not tested in the plus-maze were given a 5-min trial in the holeboard to provide a measure of locomotor activity and thus check for any sedative effects of drug treatment.

Experiment 2

Long-lasting effects of CDP during cat odor. Animals that had been treated with control injections or CDP (5 and 20 mg/kg) and exposed to cat odor in Experiment 1 were reexposed, undrugged, to the same odor 3 days later. Control-injected rats exposed to the neutral odor were also retested. Thirty

minutes after odor exposure, animals were tested in the social interaction and plus-maze tests following the same procedures described for Experiment 1.

Anxiogenic effects of PTZ. Sixty-four rats were randomly allocated between the neutral and cat odor exposure groups and exposed to the appropriate odor for 5 min (as described for Experiment 1). Immediately afterward, they were returned to the animal house. Three days later, each odor group was randomly allocated between two drug treatment groups (n = 16 in each drug treatment and odor group). They were injected with PTZ (20 mg/kg) or distilled water (control), as appropriate, and 30 min afterward tested in the social interaction test, which took place in a different room from the odor exposures. Immediately after the social interaction test, one animal of each pair was tested in the plus-maze.

RESULTS

Experiment 1

Cat odor exposure. Table 1 shows that undrugged rats exposed to cat odor made significantly fewer contacts with the odor cloth, spent less time in contact with the cloth, and spent longer sheltering under the hoppers than did rats exposed to the neutral odor. For the number of contacts with the cloth, there was a significant drug treatment × odor exposure interaction, $F(3, 110) = 6.9$, $p < 0.0005$, because all doses of CDP significantly decreased the number of contacts with the neutral but not with the cat odor cloth (see Table 1). There was also a significant drug treatment × odor exposure interaction for the time in contact with the cloth, $F(3, 110) = 9.0$, $p < 0.0001$, because CDP 20 mg/kg reduced time in contact with the neutral but not the cat odor cloth. CDP 5 mg/kg significantly increased the time in contact with both odor cloths (see Table 1).

The time spent sheltering was significantly affected by the drug treatment, $F(3, 110) = 9.9$, $p < 0.0001$, but there was no significant drug × odor interaction, $F(3, 110) = 1.5$. The time spent sheltering was increased by CDP 20 mg/kg in both groups, although on posthoc tests it reached significance only for the neutral odor group (see Table 1).

The locomotor activity scores from the holeboard showed that CDP 20 mg/kg was significantly sedative [mean (± SEM) scores: control = 230.6 ± 10.1, CDP 20 mg/kg = 36.5 ± 5.0, $p < 0.0001$]. This raised the possibility that sedative effects might be masking increased responding to cat odor. The responses during the odor exposure were therefore subjected to analyses of covariance (ANCOVAs), using the locomotor activity scores as the covariate. After these analyses, there were still no significant effects of CDP.

Social interaction. Undrugged rats previously exposed to cat odor spent significantly less time in social interaction, $F(1, 14) = 31.9$, $p < 0.0005$, made fewer rears, $F(1, 14) = 29.7$, $p < 0.0005$, and had a decreased motor activity, $F(1, 14) = 5.1$, $p < 0.05$, than rats previously exposed to the neutral odor. This result is indicative of the generalization of the phobic experience to this animal test of anxiety. CDP significantly reduced motor activity, $F(3, 26) = 28.9$, $p < 0.0001$, and therefore ANCOVA was used to analyse the effects on social interaction. CDP significantly reversed the decrease caused by cat odor exposure on the time spent in social interaction, $F(3, 25) = 3.0$, $p < 0.05$ (see Fig. 1).

Plus-maze. As observed in the social interaction test, the effects of exposure to cat odor were also generalized to the plus-maze. Undrugged rats previously exposed to cat odor had significantly lower percentage of entries on the open arms, $F(1, 14) = 5.6$, $p < 0.05$, spent less percentage of time on the open arms, $F(1, 14) = 8.6$, $p < 0.05$, and made fewer total arm entries, $F(1, 14) = 9.5$, $p < 0.01$, than rats previously exposed to a neutral odor. In the cat odor groups, CDP increased the percentage of entries onto open arms, $F(3, 28) = 3.2$, $p < 0.05$, the percentage of time spent on the open arms, $F(3, 28) = 4.5$, $p < 0.05$, and the total arm entries, $F(3, 28) = 6.6$, $p < 0.01$ (see Fig. 2).

Experiment 2

Long-lasting effects. Once again, in undrugged animals cat odor was effective at decreasing the number of contacts with the cloth, $F(1, 30) = 53.2$, $p < 0.0001$, the time spent in contact, $F(1, 30) = 108.8$, $p < 0.0001$, and the time spent sheltering, $F(1, 30) = 59.2$, $p < 0.0001$. Table 2 shows that the previous drug experience in Experiment 1 was without any significant effect on the behavioral response to cat odor in

TABLE 1

MEAN (± SEM) NUMBER OF CONTACTS AND TIME (SECONDS) IN CONTACT WITH NEUTRAL AND CAT ODOR CLOTHS AND TIME (SECONDS) SPENT SHELTERING UNDER THE FOOD HOPPER BY RATS INJECTED WITH WATER (CON) OR CDP (5, 10, OR 20 MG/KG/DAY FOR 5 DAYS)

		CDP (mg/kg/day)		
	CON	5	10	20
No. contacts				
Neutral	9.9 ± 0.5	7.5* ± 0.7	6.8** ± 0.9	2.4** ± 0.5
Cat	4.0††† ± 0.7	5.9 ± 0.9	5.0 ± 0.7	2.6 ± 0.5
Time contacts				
Neutral	144.9 ± 11.7	196.9* ± 12.3	139.8 ± 34.9	38.6** ± 11.6
Cat	37.8††† ± 5.9	80.4** ± 11.0	56.7 ± 8.4	55.5 ± 11.8
Time sheltering				
Neutral	7.3 ± 1.8	6.8 ± 2.6	6.5 ± 2.6	114.6** ± 28.3
Cat	155.5††† ± 24.1	105.2 ± 21.8	103.3 ± 21.7	180.6 ± 24.7

*$p < 0.05$, **$p < 0.01$ compared with respective control group.
†††$p < 0.001$ compared with neutral odor control group.

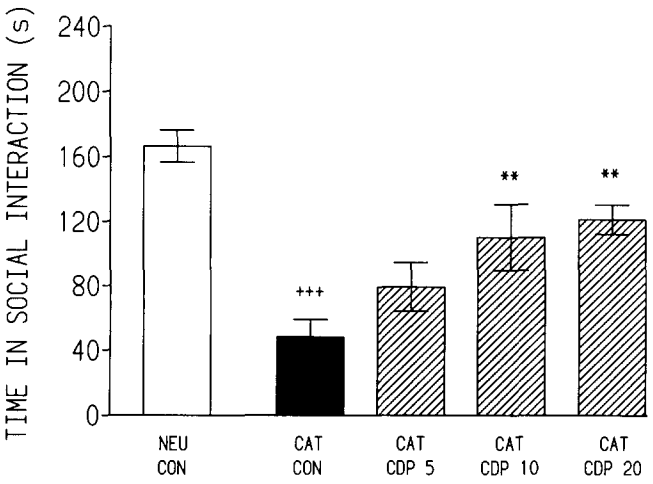

FIG. 1. Mean (±SEM) time (seconds) spent in social interaction by rats exposed to neutral and cat odor. The scores shown are the adjusted means after analysis of covariance. Rats exposed to neutral odor were previously injected with water (CON) and those to cat odor with water (CON) or chlordiazepoxide (CDP, 5, 10, or 20 mg/kg/day) for 5 days. On the test day, they were injected 30 min before odor exposures and 65 min before the social interaction test. $^{+++}p < 0.001$ compared with neutral odor control group; $^{**}p < 0.01$ compared with cat odor control group.

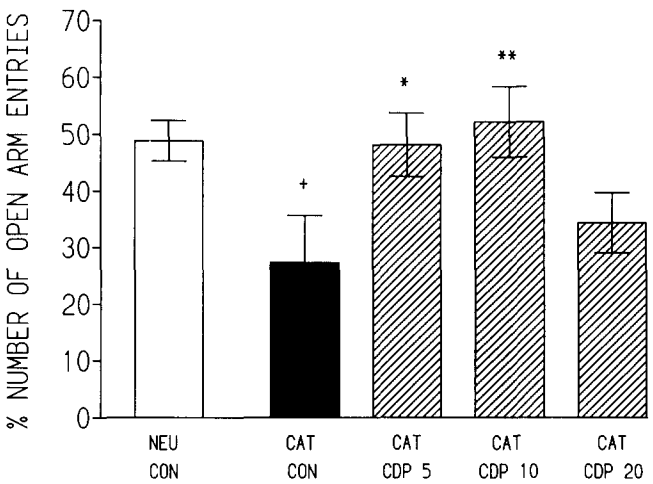

FIG. 2. Mean (±SEM) % number of entries onto open arms of the elevated plus-maze by rats exposed to neutral and cat odor. Those exposed to neutral odor were previously injected with water (CON) and those to cat odor with water (CON) or chlordiazepoxide (CDP, 5, 10, or 20 mg/kg/day) for 5 days. Animals were injected 30 min before exposure and 70 min before the plus-maze test. $^{+}p < 0.05$ compared with neutral odor control group; $^{*}p < 0.05$, $^{**}p < 0.01$, compared with cat odor control group.

Experiment 2 [odor × trial interaction, $F(2, 45) < 1.0$, for all measures].

In contrast to the responses to cat odor itself, there was clear habituation of the generalised anxiety response as measured by decreased social interaction [odor × trial interaction, $F(1, 14) = 25.2$, $p < 0.0005$]. However, the reduction in the number of rears shown by the cat odor group was still significant in Experiment 2 ($p < 0.01$), indicating less habituation of this response. No significant effect of the previous drug experience was observed on the time spent in social interaction in Experiment 2 (see Table 2). However, animals that had been injected with CDP 20 mg/kg in Experiment 1 made fewer rears ($p < 0.05$) and had lower motor activity ($p < 0.01$) in Experiment 2 when compared to other cat-exposed groups.

The effect of cat exposure on behavior in the plus-maze

TABLE 2

MEAN (±SEM) RESPONSES TO ODOR CLOTHS AND SHELTERING UNDER HOPPER FOR UNDRUGGED RATS EXPOSED FOR THE SECOND TIME TO ODORS

TRIAL 1 TRIAL 2	NEUTRAL CON CON	CAT CON CON	CAT CDP5 CON	CAT CDP20 CON
Exposure				
No contacts	9.1 ± 0.5	3.8††† ± 0.8	4.3 ± 0.7	4.6 ± 0.9
Time contact	128.0 ± 16.1	26.9††† ± 6.3	33.8 ± 7.1	35.6 ± 8.2
Time sheltering	13.3 ± 2.7	194.6††† ± 24.2	182.6 ± 20.9	185.0 ± 23.2
Social interaction				
Time spent interacting	163.1 ± 10.3	165.6 ± 14.7	155.0 ± 8.1	135.1 ± 10.3
Rears	199.5 ± 11.7	153.8†† ± 9.8	145.5 ± 15.8	98.0* ± 15.7
Motor activity	285.1 ± 6.3	268.6 ± 12.8	240.5 ± 14.5	192.3** ± 10.9
Plus-maze				
% Number	50.2 ± 5.6	33.8 ± 7.1	25.7 ± 7.6	26.6 ± 9.3
% Time	51.1 ± 8.9	21.1† ± 7.3	18.49 ± 7.1	23.3 ± 9.4
Total entries	18.1 ± 1.7	11.71† ± 2.3	9.4 ± 1.6	11.0 ± 3.0

Those exposed to cat odor had previous exposure undrugged (CON) or after 5 days of treatment with chlordiazepoxide (CDP, 5 or 20 mg/kg). Also shown are the mean (±SEM) scores in the social interaction and plus-maze tests, which took place in a separate room 30 min after exposure to odors.

$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$ compared with neutral odor control group.

$^{*}p < 0.05$, $^{**}p < 0.01$ compared with cat control group.

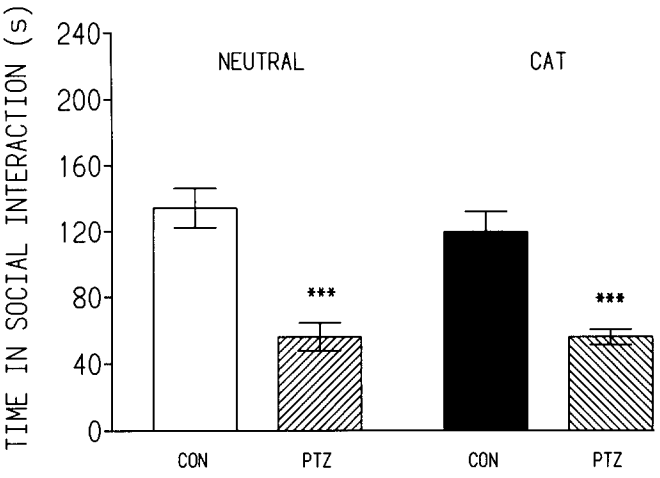

FIG. 3. Mean (±SEM) time spent in social interaction by rats tested 30 min after injection with water (CON) or with pentylenetetrazole 20 mg/kg (PTZ). Rats were exposed to neutral or cat odor 3 days before the test. ***$p < 0.001$ compared to their respective odor control group.

was maintained over trials. A significant odor effect was observed on the percentage of entries onto the open arms, $F(1, 14) = 5.2$, $p < 0.05$, and on the time spent in the open arms, $F(1, 14) = 7.3$, $p < 0.05$, and there was no significant odor × trial interaction, $F(1, 14) < 1.0$, for both measures (see Table 2). There was no significant effect of the previous drug treatment on the plus-maze scores in Experiment 2.

Anxiogenic effects of PTZ. Figure 3 shows that PTZ 20 mg/kg significantly decreased the time spent by rats in social interaction, $F(1, 28) = 52.1$, $p < 0.0001$, but that the odor experience prior to the test was not important, $F(1, 28) < 1.0$. Similarly, the percentage of entries onto and the percentage of time spent on the open arms was significantly decreased by PTZ, $F(1, 28) = 4.7$ and 6.8, $p < 0.05$, respectively, but there was no odor × PTZ interaction, $F(1, 28) < 1.0$, for both measures.

DISCUSSION

CDP had a weak effect on the behaviors of rats during exposure of cat odor. The lowest dose was able to increase the time spent in contact with the cloth but not the frequency of these contacts, nor did it decrease the time spent sheltering. A clear sedative effect was observed in the holeboard with CDP 20 mg/kg but this did not seem to be significantly masking any increased responses to cat odor. However, it seemed that cat odor did significantly reduce the sedative actions of CDP 20 mg/kg. The lack of a consistent CDP effect during exposure to cat odor is in keeping with our previous results (6). Blanchard et al. (2) also reported no effects, other than those probably attributable to sedation, of diazepam on the behavior of rats exposed to cat odor.

CDP was fully effective in counteracting the generalised anxiety responses detected in the social interaction and plus-maze tests. This raises the possibility that the responses during actual odor exposure reflect a phobic anxiety state, whereas those subsequently expressed in the plus-maze and social interaction tests may reflect a more generalised state of anxiety.

Exposure to the threatening stimulus under the effect of an anxiolytic drug did not change the behavior of animals when reexposed, undrugged, to the same phobic stimulus 3 days later, nor was a different anxiogenic stimulus (an anxiogenic dose of PTZ) able to reevoke the internal state generated by the exposure of cat odor and measured in the plus-maze and social interaction tests.

Further experiments are clearly needed to establish whether the behavioral responses evoked by the odor of a predator can indeed be used as an animal test of a phobic anxiety state. From the work of the Blanchards' group, it is clear that benzodiazepines have little effect on wild and laboratory rats' fear responses to the actual presence of a predator (3,4). Mineka (8) distinguished two clear components of a phobic response: behavioral avoidance and behavioral disturbance. We consider that the responses we measured during cat odor exposure reflected avoidance of that odor. The behaviors measured in the Blanchards' experiments may be more reflective of the behavioral disturbance caused by predator odor and these were reduced by relatively high doses of diazepam. Thus, these actions of diazepam could either have reflected its sedative effects or suggested that the benzodiazepines would be more effective against the behavioral disturbances caused by a phobic situation than they are against phobic avoidance.

The present results allied with other evidence from this laboratory indicates that exposure to cat odor may be a useful method for generating and detecting phobic reactions in rats.

ACKNOWLEDGEMENTS

The authors are grateful to Pei Ying Wu and Fiona Sanders for expert technical assistance. These experiments were supported by grants from the Wellcome Trust and Conselho Nacional de Desenvolvimento Cientifico e Tecnologico, Brasil.

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