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Effect of Diazepam on Successive Negative Contrast in One-Way Avoidance Learning

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MORALES, A., M. D. C. TORRES, J. L. MEGIAS, A. CANDIDO AND A. MALDONADO. *Effect of diazepam on successive negative contrast in one-way avoidance learning.* PHARMACOL BIOCHEM BEHAV **43**(1) 153–157, 1992.— The effect of administration of diazepam on successive negative contrast in one-way avoidance learning was examined in rats. Contrast was induced by shifting rats from a large reward, 30 s spent in the safe compartment, to a small reward, 1 s spent in the safe compartment. IP administration of 2 mg/kg diazepam eliminated this negative contrast. Moreover, this effect is dose dependent, with doses of 2 and 2.5 mg/kg, but not 0.5 mg/kg, effective in reliably reducing contrast. These results suggest the existence of similar or common underlying mechanisms in both aversive and appetitive contrast effects; they are discussed in light of the current theories of frustrative nonreward and as a mean of studying the behavioral and biological mechanisms of anxiety.

Anxiety Benzodiazepine Diazepam One-way avoidance Successive negative contrast

THE successive negative contrast effect was initially described in appetitive instrumental learning tasks (6). Basically, this effect can be obtained by training one group of animals to undertake a task under a large amount of reinforcement; a sudden reduction in the amount of reinforcement results in a substantial impairment in the performance of the learned response, being inferior to that of control subjects that received a short amount of reward throughout the experiment (6). This negative contrast effect has also been extensively studied from a pharmacological point of view. In this way, anxiolytic substances, mainly benzodiazepines, barbiturates, and ethanol, reduce and sometimes eliminate this contrast effect (11,13,14).

A similar contrast effect has been demonstrated in consummatory behavior, in which chlordiazepoxide, a benzodiazepine drug, also eliminates the negative contrast effect that occurs when food-deprived rats are shifted from a 32 to a 4% sucrose solution (10). This effect is only produced when the drug is administered during the second postshift day, but not during the first (12,26).

Recently, a similar successive negative contrast effect has been described in one-way avoidance learning (4). In this procedure, subjects are exposed to two markedly different compartments or places. In one, the danger compartment, they receive a warning signal followed by electric foot-shock. In the other, the safe compartment, the warning signal or the shock never appear. Subjects placed in the danger compartment learn to run into the safe compartment when the warning signal is turned on and so learn to avoid the shock (20). With this task, a successive negative contrast situation has been arranged recently (4): Briefly, once subjects have acquired the avoidance response with the time spent in the safe compartment being 30 s (preshift period), this time was reduced to 1 s (postshift period). The performance of this group was compared to that of one control group in which the time spent in the safe compartment remained constant (1 s) during both the pre- and postshift periods. The results of this study showed that a) performance of the shifted group (first group) on the postshift period was inferior to that observed in the nonshifted group (second group), b) this effect could not be explained by the differences between the groups in the intertrial interval (ITI) or the number of trials required in the preshift period, and, finally, c) this contrast effect could be obtained with different unconditioned stimulus (electric foot-shock) intensities. These results are, consequently, similar to those described earlier in appetitive tasks.

Previously, some authors found that time spent in the safe compartment had reinforcing properties so learning was enhanced when more time was spent in that compartment (3,5,7,16,23,24).The results obtained in the contrast effect

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with the one-way avoidance procedure (4) also suggest that the time spent in a safe place acts as a reinforcer of the one-way avoidance response and that it may be functionally equivalent to appetitive reinforcers. Subsequently, if this successive negative contrast effect in one-way avoidance learning is similar to that observed in instrumental conditioning and consummatory behavior (10,13) it should also be possible to eliminate it with anxiolytic drugs.

The main aim of the present work has been to study the effect of diazepam, an anxiolytic drug, on the successive negative contrast effect in one-way avoidance learning. The experiment is described in three different parts. In the first part, we study the action of diazepam, with a dose of 2 mg/kg, upon the successive negative contrast effect in one-way avoidance learning previously referred (4). Consistent with the results obtained in appetitive conditioning and consummatory behavior, this drug should reduce the typical impairment in performance in the contrast group (shift group). Second, we analyze the possible dose-dependent action of diazepam. Finally, in the third part, we study the possibility that diazepam not only affects the contrast effect but also the one-way avoidance task.

Our study has two important theoretical implications: First, if a benzodiazepine (diazepam) eliminates the contrast effect in one-way avoidance learning as they do in the appetitive and consummatory cases, it would suggest the existence of similar or common underlying mechanisms in both aversive and appetitive learning (4,8,18,22); second, our results may validate this contrast effect as a new animal model of anxiety.

METHOD

Subjects

Fifty-six female Wistar rats, weighing 180–220 g, were used. Rats were housed individually with food (Sandersmus, Spain) and tapwater ad lib. Room temperature was kept to about 20°C with lights on from 0800–2000h. The whole experiment took place during the light phase, between 0900–1400h.

Apparatus

A one-way avoidance chamber and LETICA control apparatus were used. The avoidance chamber consisted of two equal compartments 27 × 25 × 28 cm, made of Plexiglas. The compartments were separated by a 0.5-cm thick partition 25 × 28 cm, with a square 9 × 9 cm hole and a removable gate to allow communication between compartments. Both compartments thus had the same dimensions and were made of the same material except the danger compartment was fitted with a grid floor. The grid floor consisted of 19 stainless steel rods 4 mm in diameter and spaced 2 cm apart center to center connected in series to a LETICA LI-2900 module capable of delivering a continuous scrambled shock. The floors in both compartments were hinged to operate a microswitch when depressed; this allowed the control of apparatus, procedure, and responses by a PC-XT microcomputer. A speaker was placed in the middle of the lateral wall so that half of it was oriented to the danger compartment and the other half to the safe compartment. The warning signal was a 2,000-Hz tone of 88-db sound pressure level (SPL). The roof of the danger compartment consisted of a black glass panel, which was only removed to put the subject into the chamber. A rigid, non-transparent white plastic transportation box, 24 × 14 × 19 cm, was placed in the safe compartment in contact with the communication hole. This box was used as the safe compartment and to move the rat when safe time was completed. The transportation box had a carrying handle on top and had no wall on the side in contact with the partition of the avoidance chamber and, therefore, with the communication hole and gate. The floor, ceiling, and walls of this box were made of the same material. An air extractor was installed outside the avoidance chamber. This produced a background noise of 70-db SPL.

Procedure

On the experimental day, rats were removed from their cages and lightly handled for about 1 min; they were then injected either with diazepam or vehicle and returned to the cages for the next 30 min. Once this time had elapsed, rats were put into the avoidance chamber and allowed 5 min to explore both compartments without interference in the presence of the background noise. Thereafter, the communication gate was closed, shutting the rat in the danger compartment, and then the trials began. Each trial consisted of a warning signal followed after 5 s by an electric foot-shock of 1 mA. Both the warning signal and the shock continued until the animal moved into the safe compartment or until 30 s had elapsed. The gate between the two compartments was opened as soon as the warning signal sounded and closed when the rat entered the safe compartment. Time in the danger compartment before the onset of the warning signal was the same for all experimental conditions (15 s). Once the safe time had been completed, the transportation box was lifted over the apparatus and the rat was turned out into the danger compartment. This took only from 1–2 s. The box was then replaced in the safe compartment of the avoidance chamber.

All rats were trained until they reached five consecutive avoidance responses in the preshift phase and eight consecutive avoidance responses in the postshift phase. The avoidance response was considered to have taken place when the animal moved into the safe compartment within 5 s after onset of the warning signal. Once five consecutive avoidance responses had been achieved, the postshift phase began. This consisted of exactly the same procedure as the preshift phase except the time in the safe compartment was shifted in some cases according to each experimental condition. The postshift phase continued until rats reached eight consecutive avoidance responses.

Subjects were randomly assigned to seven groups (n = 8) (see Table 1). Group 30-1/V (V = injected with vehicle) was exposed to 30 s in the safe compartment in the preshift phase and to 1 s in the postshift phase. This safe time remained constant throughout the experimental session as 1 s for Group 1-1/V and as 30 s for Group 30-30/V. In this way, we can replicate the basic contrast effect, comparing the results of Group 30-1/V with Groups 1-1/V and 30-30/V. Group 30-1/2mg received the same treatment as Group 30-1/V except the former was IP injected with 2 mg/kg diazepam and the latter with vehicle.

Moreover, we studied the possible dose-dependent effect of diazepam upon this negative contrast with Groups 30-1/0.5mg and 30-1/2.5mg: these two groups were exposed to the same experimental procedure as Group 30-1/2mg but now the doses of diazepam being 0.5 and 2.5 mg/kg, respectively.

Finally, with the aim of studying the possible influence of diazepam upon the avoidance task employed we introduced Group 1-1/2mg, in which subjects received IP administration of 2 mg/kg diazepam but equal times spent in the danger/safe compartments as Group 1-1/V (injected with vehicle) (see Table 1).

TABLE 1

TIME SPENT (SECONDS) IN THE SAFE AND DANGER COMPARTMENTS DURING PRE- AND POSTSHIFT PHASES BY EACH GROUP AND TREATMENT (DIAZEPAM OR VEHICLE)

		Preshift Phase		Postshift Phase		
Groups	*n*	Safe	Danger	Safe	Danger	Treatment
30-1/V	8	30	15	1	15	Vehicle
1-1/V	8	1	15	1	15	Vehicle
30-30/V	8	30	15	30	15	Vehicle
30-1/2mg	8	30	15	1	15	Diazepam (2.0 mg/kg)
30-1/0.5mg	8	30	15	1	15	Diazepam (0.5 mg/kg)
30-1/2.5mg	8	30	15	1	15	Diazepam (2.5 mg/kg)
1-1/2mg	8	1	15	1	15	Diazepam (2.0 mg/kg)

Dependent Variable

The dependent variable used was the number of trials needed to reach the acquisition criteria in each phase. There were two criteria employed: a) in the preshift phase number of trials to achieve five consecutive avoidance responses and b) in the postshift phase number of trials to achieve eight consecutive avoidance responses.

Statistical Analysis

Values reported are means (±) SEM Scores in each criterion were submitted to a Kruskal–Wallis test for global significance. Comparisons between the different groups were performed using a Mann–Whitney *U*-test.

Drug

Diazepam (kindly donated by Productos Roche, Spain) was suspended in a 1% Tween-80 (Sigma, Spain) saline solution (vehicle) and IP administered. Volume of administration was 10 ml/kg.

RESULTS

Overall analysis of the results showed statistically significant differences among groups in preshift, $H(6) = 16.09$, $p < 0.01$, and postshift phases, $H(6) = 18.28$, $p < 0.005$. The results can be seen in Table 2.

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Preshift phase. The mean number of trials needed to reach criterion in Groups 30-1/V, 1-1/V, 30-30/V and 30-1/2mg are illustrated in Fig. 1. Inspection of this figure shows that all groups in the preshift phase required similar numbers of trials to reach criterion. Statistical analyses confirmed this observation without significant differences among them.

Postshift phase. As illustrated in Fig. 1, in the postshift phase Group 30-1/V appeared to need more trials to reach criterion than the other three groups (see also Table 2). Statistical analysis revealed, first, that Group 30-1/V required more trials than Group 1-1/V ($U = 3$, $p < 0.001$), indicating a clear contrast effect in one-way avoidance learning. Moreover, and as expected, this contrast effect was not manifested in Group 30-30/V, which differs from Group 30-1/V ($U = 7$, $p < 0.007$) but not from Group 1-1/V ($U = 29$, n.s.). Second, although there were no significant differences between Groups 30-1/2mg and 30-1/V in the preshift phase they were statistically different in the postshift phase ($U = 13.5$, $p < 0.05$), indicating that IP administration of 2 mg/kg diazepam reliably reduced the contrast effect. Groups 30-1/2mg, 1-1/V, and 30-30/V did not differ significantly in this phase.

TABLE 2

MEAN NUMBER OF TRIALS (±SEM) TO REACH CRITERIA OF ACQUISITION IN THE PRE- AND POSTSHIFT PHASES BY EACH GROUP

Groups	Preshift Phase	Postshift Phase
30-1/V	7.1 (1.3)	12.5 (2.3)
1-1/V	8.5 (1.4)	2.5 (0.9)
30-30/V	7.6 (1.3)	3.8 (1.6)
30-1/2mg	7.4 (2.5)	6.4 (1.7)
30-1/0.5mg	4.6 (0.9)	10.1 (4.1)
30-1/2.5mg	11.0 (1.5)	4.7 (2.0)
1-1/2mg	13.5 (2.0)	2.4 (0.9)

Dose-Dependent Effect of Diazepam

Now we will examine the possible dose-dependent effect of diazepam upon the successive negative contrast effect in one-way avoidance learning. The groups of interest in this

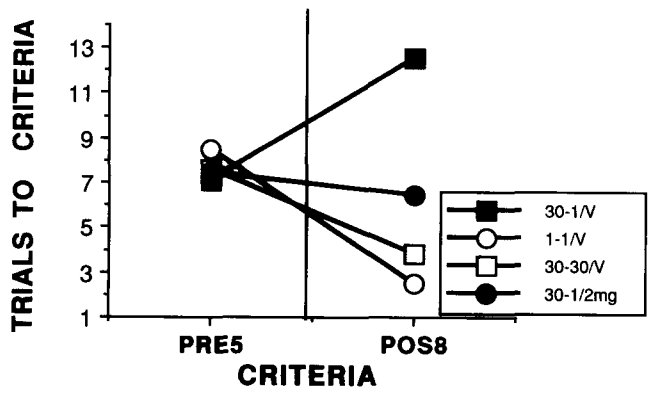

FIG. 1. Mean number of trials to reach criteria of acquisition in the pre- and postshift phases by each group (30-1/V, 1-1/V, 30-30/V, 30-1/2mg). In each group, each pair of numbers stands for time in the safe compartment during the first and second phases, respectively. V, injected with vehicle; 2mg, injected with 2 mg/kg diazepam.

respect are 30-1/2mg, 30-1/0.5mg, 30-1/2.5mg, 30-1/V, and 1-1/V. No possible comparison between these groups was statistically significant in the preshift phase. Figure 2 illustrates the mean number of trials needed to reach the criterion in the postshift phase. It appears from this figure that the effect of diazepam upon the successive negative contrast in one-way avoidance learning is dose dependent, with doses of 2 and 2.5 mg/kg, but not 0.5 mg/kg, effective in reliably reducing it. These observations were confirmed by statistical analyses. So, there were no significant differences either among Group 1-1/V with Groups 30-1/2mg and 30-1/2.5mg (U = 15 and U = 28.5, respectively, n.s.) or between 30-1/2mg and 30-1/2.5mg (U = 24.0, n.s.). Similarly, no significant differences were observed between 30-1/V and 30-1/0.5mg (U = 22.0), but statistical analyses revealed significant differences between any of the first three groups (30-1/2mg, 30-1/2.5mg, and 1-1/V) compared with Groups 30-1/0.5mg and 30-1/V.

Effect of Diazepam on the One-Way Avoidance Task

With the aim of discovering if diazepam exerted some effect on the one-way avoidance task itself, we administered it in a dose of 2 mg/kg to Group 1-1/2mg. This group was given the same safe times as Group 1-1/V so they could be compared to find out the effect of diazepam over the task. The statistical analyses conducted revealed no significant differences between Group 1-1/2mg and Group 1-1/V in both preshift (U = 15.5, n.s.) and postshift (U = 29, n.s.) phases.

DISCUSSION

The results obtained in the present experiment, first, replicate those previously reported by our group elsewhere, that is, when time spent in the danger compartment is held constant a shift from a large reward (i.e., more time spent in the safe compartment) to a small reward (less time) produced a negative contrast effect in the shifted group compared to a small reward nonshifted control group. Second, our results demonstrate that diazepam, in doses of 2 and 2.5 mg/kg, eliminates the successive negative contrast effect in one-way avoidance learning. The effect of diazepam exhibits dose dependency because it is effective with doses of 2 and 2.5 mg/kg but not 0.5 mg/kg. Regarding the 2.5-mg/kg dose, it has to be noted that, although not significant, in the preshift phase the number of trials needed to reach criterion was higher in Group 30-1/2.5mg than in Group 30-1/V. This could be due to the sedative effect of diazepam in high doses, which obviously interferes with the acquisition of a predominantly motor response. In fact, pilot studies carried out in our laboratory showed that doses of 4 mg/kg clearly impaired the acquisition phase due to the sedative effect (data not shown). And, finally, our results show that diazepam did not affect either acquisition of the one-way avoidance response (preshift phase) or maintenance of this response (postshift phase), as can be seen comparing Groups 1-1/2mg and 1-1/V, thus replicating data of other authors (13). These two groups received the same treatment with the exception that Group 1-1/2mg was injected with 2 mg/kg diazepam and Group 1-1/V with vehicle.

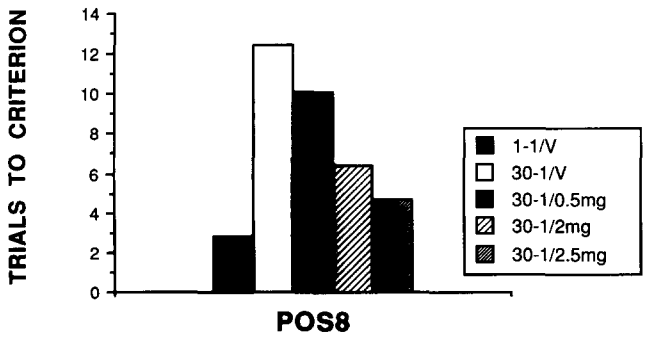

FIG. 2. Mean number of trials to reach criterion in the postshift phase by each group (30-1/V, 1-1/V, 30-1/2mg, 30-1/0.5mg, 30-1/2.5mg). In each group, each pair of numbers stands for time in the safe compartment during the first and second phases, respectively. V, injected with vehicle; 2mg, injected with 2 mg/kg diazepam; 0.5mg, injected with 0.5 mg/kg diazepam; 2.5mg, injected with 2.5 mg/kg diazepam.

These data are in accordance with the literature, where benzodiazepines eliminate the negative contrast effects induced a) in appetitive instrumental conditioning (13,14) and b) in consummatory behavior (10,11). It is also important to note that diazepam only affected the postshift phase and did not alter the results of the preshift phase; we can than conclude that in our experiments the drug did not affect the task, as reported in other studies (13,25). This last point is important because a significant increase in the number of trials needed in the preshift phase could be responsible for the attenuation of the contrast effect (e.g., due to a better learning). But, this is not our case, as can be seen by comparing Groups 30-1/V vs. 30-1/2mg, showing significant differences in the postshift phase but not in the preshift phase.

One possible explanation of the effect of diazepam in our experiment rests in part on that given for the negative contrast effect in one-way avoidance learning. Considering that the time spent in safe places may act as an appetitive reinforcer or incentive, the reduction of time in safety could produce a central frustration state accompanied by an emotional response (1,2,19), probably similar to an anxiety state (15). In this typical frustrative nonreward situation, diazepam would induce an anxiolytic effect, reinstating the animal's response in spite of the reward reduction (15). Similarly, it has been observed that anxiolytics slow extinction processes in appetitive tasks when reward is no longer available (13,21).

A second possible interpretation of our results implies that several physiological processes may be triggered by the reduction in the amount of reinforcement—safe time (11). The downshift in the time spent in the safe place may give rise to processes of detection of the new reinforcer—1 s— and comparison with the memory of the preshift one—30 s. These processes, together with a complementary evaluation process, would induce the animal to enter a conflict stage: to reach the safe compartment because of its new absolute incentive value—1 s— or avoid it because of its poor relative rewarding properties compared with the preshift incentive—30 s. It is this conflict stage that would be eliminated by administration of diazepam in accordance with most current animal models of anxiety that imply conflict situations (11).

In other respects, it is important to note that both response to anxiolytic substances and any response in anxiety tests could be a gender-related phenomenon. In this regard, it has been observed that there is a higher sensibility to diazepam on the burying behavior test in male rats as compared to females (9). Both genders differ even in the responses given in different anxiety tests with no pharmacological treatment (17). In our study, we only used female rats with the goal of reproducing exactly the contrast conditions previously described (4); in any

case, it should be interesting to test if there is any difference in the action of diazepam over the contrast effect when using male rats. Equally, whether the estrous cycle phases in females has any bearing on this effect should be studied; in this respect, and in the burying behavior test, the anxiolytic effect of diazepam (0.5 mg/kg) is related to that cycle, proestrus females being more reactive than metestrus females, although significant differences between both groups could not be detected with higher doses (9). Because in our study the effective doses were 2.0 and 2.5 mg/kg, the influence of the estrous cycle seems to be an irrelevant factor.

To summarize, IP administration of 2.0 or 2.5 mg/kg, but not 0.5 mg/kg, eliminates the successive negative contrast effect in one-way avoidance learning in female rats. Although speculative, we can suggest that the elimination of this contrast effect may be due to the antifrustrative or anticonflict action of diazepam, lowering the anxiety levels associated with a reduction in the time spent in the safe compartment. Then, our results point to the existence of similar or common underlying mechanisms in both aversive and appetitive learning (4,8,18,22) and propose this contrast effect in aversive conditioning as a new animal model of anxiety.

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