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Successive negative contrast in one-way avoidance: effect of thiopental sodium and chlorpromazine

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Abstract

The successive negative contrast effect on one-way avoidance was induced by shifting rats from a large reward (30 s spent in the safe compartment after completion of the avoidance response, pre-shift phase) to a small reward (1 s, post-shift phase). Under these conditions, the previously learned avoidance response deteriorated (negative contrast) when compared to a control group for which 'safe time' remained constant throughout the experimental situation (1 s). Thiopental sodium at a dose of 5 or 10 mg/kg, but not at 1, 2, 15 or 20 mg/kg i.p., abolished the negative contrast effect, and did not affect performance of the one-way avoidance task. Similar results were found when rats were treated with diazepam (1 mg/kg i.p.). Chlorpromazine at a dose of 0.5 or 1 mg/kg i.p. did not affect negative contrast, although at higher doses (2 or 3 mg/kg) there was an increase in the number of trials needed to reach the criterion for learning the avoidance response. This increase was evident in both pre-shift and post-shift phases, although only in the experimental situations involving a low level of reinforcement (1 s in the safe compartment). On the basis of these results, we tentatively suggest that the successive negative contrast effect in one-way avoidance in rats can be considered a useful pharmacological animal model for research into anxiety.

Keywords: Animal model; Anxiety; Chlorpromazine; Diazepam; One-way avoidance; Successive negative contrast; Thiopental sodium

1. Introduction

Many psychological and psychobiological studies have demonstrated the importance of animal models in elucidating normal and pathological human behavior (Miller, 1985). In the context of anxiety studies, Treit (1985, 1991) has proposed that animal models should fulfil three requirements: (1) pharmacological correlation, i.e., the model should be sensitive to anxiolytic substances used in clinical practice, but insensitive to non-anxiolytic substances; (2) isomorphism, i.e., the 'anxiety response' used by the model should be similar to responses observed in humans; and (3) homology with regard to the external or internal causes that trigger anxiety responses.

Research by our group during the last years has aimed to characterize the successive negative contrast effect in one-way avoidance tasks, and to develop this approach as a useful animal model for the study of substances with anxiolytic activity. In the one-way avoidance task, experimental subjects (rats) learn a one-way avoidance response, followed by a period of 30 s (pre-shift period) in a so-called 'safe compartment' before continuing to the next trial. Once the avoidance response has been acquired, the 'safe time' is abruptly reduced to 1 s (post-shift period). This manipulation leads to a clear impairment of the previously learned avoidance response (negative contrast) in comparison to that of animals trained with a 1-s safe period during the entire experimental session (control, unshifted group) (Cándido et al., 1992).

In general, the successive negative contrast effect, initially described in reports of appetitive studies (see Crespi, 1942) and later, studies of drinking behavior (Flaherty, 1982), has been associated with a negative emotional reaction (frustrative non-reward) arising from the sudden loss of reinforcement (Amsel, 1958). This approach raised the possibility that negative contrast could be abolished pharmacologically, as subsequent studies indeed seemed to show. For example, results with the theoretical model of anxiety developed by Gray (1982) suggested that the emotional response associated with loss of an expected reinforcement could be abolished by the administration of

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anxiolytic drugs such as benzodiazepines, barbiturates and ethanol (see Gray, 1977, and Flaherty, 1990, for a review). Moreover, Flaherty (1991) has proposed that the successive negative contrast seen in drinking behavior tasks can be considered an animal model of anxiety.

The theoretical explanation of the successive negative contrast effect in avoidance is based on an emotional process associated with a sudden reduction in the time spent in the safe compartment. Within the context of frustrative non-reward, time in the safe compartment acts as a second source of reinforcement in addition to the reduction of fear that accompanies the avoidance response (Cándido et al., 1984, 1989; Denny, 1971; Masterson and Crawford, 1982). The loss of reinforcement gives rise to a situation of frustrative non-reward similar to that described for (for example) appetitive tasks, and different from the fear that arises from the use of an aversive stimulus. From this perspective, the negative contrast task we now investigated should be sensitive to the action of anxiolytic substances, which should not affect the conditioning of avoidance (pre-shift phase). Diazepam, through its effect on the γ-aminobutyric acid type A receptor system ($GABA_A$), abolishes negative contrast in a dose-dependent way (Morales et al., 1992; Torres et al., 1994), while buspirone, an anxiolytic that acts through the serotonergic system, does not have this effect (Torres et al., 1995). The present experiment was designed in accordance with the criteria proposed by Treit (1985, 1991), with particular attention to the pharmacological correlation, in an attempt to validate the experimental situation described here as an approach for the study of anxiolytic substances. Our objectives were, firstly, to determine whether negative contrast in one-way avoidance (as in appetitive (Gray, 1977) and drinking behavior tasks (Flaherty and Driscoll, 1980; Flaherty et al., 1982) was abolished by thiopental sodium, a barbiturate that, like diazepam, acts specifically on the $GABA_A$ receptor system (Macdonald and Olsen, 1994). Secondly, we set out to evaluate the sensitivity of negative contrast to non-anxiolytic drugs such as chlorpromazine, a neuroleptic that acts preferentially through the dopamine D_2 receptor (Seeman, 1995) and has no effect in similar negative contrast situations (Rosen and Tessel, 1970; Flaherty et al., 1992). The lack of effect of chlorpromazine would constitute further evidence that our model of negative contrast in one-way avoidance is indeed selective for the action of anxiolytic drugs.

2. Materials and methods

2.1. Experiment 1

This experiment tested the effect of thiopental sodium, a barbiturate drug, on successive negative contrast in one-way avoidance learning. The results were compared to those obtained in a group of animals receiving diazepam.

2.1.1. Animals

In total, 90 female Wistar rats, weighing 185–230 g, were used in this experiment. The rats were housed individually with food (Panlab, Spain) and tap water available ad libitum. Room temperature was kept at about 20°C with lights on from 08:00 to 20:00 h. The entire experiment took place during the light phase, between 09:00 and 14:00 h.

2.1.2. Apparatus

A Letica one-way avoidance chamber was used. The avoidance chamber consisted of two equal compartments 27 cm long × 25 cm wide × 28 cm high, made of Plexiglas. The compartments were separated by a 0.5 cm thick partition 25 cm wide × 28 cm high, with a square 9 × 9 cm hole and a removable gate to allow movement between compartments. Both compartments thus had the same dimensions and were made of the same material, except that 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 floor in both compartments was hinged to operate a microswitch when depressed; this allowed the apparatus, procedure and responses to be controlled by a PC-XT microcomputer. A speaker was placed in the middle of the lateral wall so that half was oriented to the danger compartment and the other half to the safe compartment. The warning signal was a 2000 Hz tone of 88 dB. The roof of the danger compartment consisted of a black glass panel, which was removed only to put the rat into the chamber. A rigid, non-transparent white plastic carrying box 24 cm long × 14 cm wide × 19 cm high 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 the safe time was completed. The carrying box had a handle on top and 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 installed outside the avoidance chamber produced a background noise of 70 dB.

2.1.3. Procedure

On the day of the experiment, the rats were removed from their cages and lightly handled for about 1 min. They were then injected with various drugs, according to the different experimental conditions (see below), and returned to the cages for the next 30 min. Once this time had elapsed, the rats were placed in 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 to shut the rat in the danger compartment, and the trials then began. Each trial consisted of a warning signal followed 5 s later

by a 1-mA electric foot-shock. 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. The time spent in the danger compartment before the start 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 out of the apparatus and the rat was turned out into the danger compartment. This took from 1 to 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 pre-shift phase and eight consecutive avoidance responses in the post-shift phase. An avoidance response was considered to have taken place when the animal moved into the safe compartment within 5 s after the start of the warning signal. Once five consecutive avoidance responses had been achieved, the post-shift phase began. It consisted of trials conducted as during the pre-shift phase, except that the time in the safe compartment was changed from 30 to 1 s for several groups of rats. The post-shift phase continued until rats reached eight consecutive avoidance responses. These criteria were selected according to results of our earlier studies. The entire procedure was carried out in a single session with each rat (Cándido et al., 1992; Morales et al., 1992).

Rats were randomly assigned to ten groups ($n = 9$). Thus, group 30-1/vehicle (injected with vehicle) spent 30 s in the safe compartment during the pre-shift phase and 1 s in the post-shift phase. This safe time (1 s) remained constant throughout the experimental session for group 1-1/vehicle. Group 30-1/diazepam, on the other hand, received the same treatment as group 30-1/vehicle, except that animals in the former group were i.p. injected with diazepam (1 mg/kg).

The six experimental groups treated with thiopental sodium were group 30-1/thiopental-1, 30-1/thiopental-2, 30-1/thiopental-5, 30-1/thiopental-10, 30-1/thiopental-15 and 30-1/thiopental-20. All groups were treated as described for group 30-1/vehicle, except that thiopental sodium was injected i.p. at a dose of 1, 2, 5, 10, 15 or 20 mg/kg, respectively.

Finally, to study the possible influence of thiopental sodium on the avoidance task, we used a group (1-1/thiopental-5) in which subjects received i.p. 5 mg/kg thiopental sodium, but the times spent in the danger/safe compartments were the same as for group 1-1/vehicle.

2.1.4. Dependent variable

The dependent variable used was the number of trials needed to reach the acquisition criterion in each phase. There were two criteria: number of trials to achieve five consecutive avoidance responses in the pre-shift phase, and number of trials to achieve eight consecutive avoidance responses in the post-shift phase. Each criterion was taken as met at the first of each sequence of consecutive responses.

2.1.5. Statistical analysis

Values are reported as means ± S.E.M. Scores for each criterion were analyzed with the Kruskal-Wallis test for global significance. Comparisons between the different groups were done using the Mann-Whitney U-test.

2.1.6. Drugs

Thiopental sodium (Sigma) was prepared in isotonic saline, which was used as the vehicle solution. Diazepam (kindly donated by Productos Roche, Spain) was suspended in a 1% Tween-80 (Sigma, Spain) saline solution. Both drugs were administered i.p. The volume administered was 10 ml/kg.

2.2. Experiment 2

The main aim of this experiment was to test the effect of chlorpromazine, a neuroleptic drug, on successive negative contrast in one-way avoidance learning.

2.2.1. Animals

In total, 64 female Wistar rats, weighing 185–230 g, were used in this experiment. Housing and maintenance were as described for experiment 1. The entire experiment also took place during the light phase, between 09:00 and 14:00 h.

2.2.2. Apparatus

As described in experiment 1.

2.2.3. Procedure

The rats were randomly assigned to eight groups ($n = 8$ except in group 1-1/chlorpromazine-3, where $n = 9$) and subjected to the same procedure as described for experiment 1, except that now chlorpromazine was used. In this case, however, and as in a previous study (Flaherty et al., 1992), a time of 120 min elapsed between the injections and the start of the experimental session. Under these conditions, group 30-1/vehicle and 1-1/vehicle were as described in experiment 1. The four experimental groups treated with chlorpromazine were groups 30-1/chlorpromazine-0.5, 30-1/chlorpromazine-1, 30-1/chlorpromazine-2 and 30-1/chlorpromazine-3. All groups were treated as described for group 30-1/vehicle, except that now chlorpromazine was injected i.p. at a dose of 0.5, 1, 2 or 3 mg/kg, respectively.

Finally, to study the possible influence of chlorpromazine on the acquisition or maintenance of the avoidance task, we used two additional groups, namely 30-30/chlorpromazine-3 and 1-1/chlorpromazine-3. In the former, the subjects received i.p. 3 mg/kg chlorpromazine, and spent 30 s in the safe compartment throughout the experimental

session (unshifted group); in the latter, 3 mg/kg i.p. chlorpromazine was injected, but the rats were subjected to the same experimental conditions as for group 1-1/vehicle.

2.2.4. Dependent variable

As in experiment 1.

2.2.5. Statistical analysis

As in experiment 1.

2.2.6. Drugs

Chlorpromazine (Sigma), prepared in isotonic saline, which was used as the vehicle solution, was administered i.p. in a volume of 10 ml/kg.

3. Results

3.1. Experiment 1

Overall analysis of the results showed no statistically significant differences between groups in the pre-shift phase ($H(9) = 10.88$, n.s.). In the post-shift phase, however, statistically significant differences between groups were obtained ($H(9) = 20{,}39$, $P < 0.01$). The results are summarized in Table 1.

3.1.1. Effect of diazepam

The mean number of trials needed to reach the pre-shift and post-shift criteria in groups 30-1/vehicle, 1-1/vehicle and 30-1/diazepam are shown in Table 1. In the pre-shift phase, no statistically significant differences were obtained between groups 1-1/vehicle, 30-1/vehicle and 30-1/diazepam. In the post-shift phase, however,significant differences were obtained between group 30-1/vehicle and groups 1-1/vehicle ($U = 9.5$, $P < 0.003$) and 30-1/diazepam ($U = 12{,}5$, $P < 0.008$), respectively, but not between group 30-1/diazepam and group 1-1/vehicle ($U = 33$, n.s.). These results replicate the successive negative contrast effect in one-way avoidance learning (Cándido et al., 1992), and the attenuation of this effect on administration of diazepam (Morales et al., 1992).

Table 1
Effect of diazepam and thiopental sodium

Group	Pre-shift phase	Post-shift phase
30-1/vehicle	7.1 (1.0) ^{ns}	13.3 (3.2) ^{b}
1-1/vehicle	9.7 (1.6) ^{NS}	4.2 (1.2) ^{a}
30-1/diazepam	8.6 (1.8) ^{NS,ns}	4.1 (1.7) ^{a,ns}
30-1/thiopental-1	5.9 (0.8) ^{NS}	16.1 (5.0) ^{NS}
30-1/thiopental-2	4.9 (0.6) ^{NS}	8.4 (2.0) ^{NS}
30-1/thiopental-5	6.9 (1.6) ^{NS,ns}	3.9 (2.8) ^{a,ns}
30-1/thiopental-10	7.1 (1.3) ^{NS,ns}	6.7 (3.5) ^{a,ns}
30-1/thiopental-15	3.5 (2.9) ^{NS}	9.5 (3.8) ^{NS}
30-1/thiopental-20	7.4 (1.2) ^{NS}	13.1 (4.9) ^{NS}
1-1/thiopental-5	8.8 (1.5) ^{ns}	3.4 (1.1) ^{ns}

Mean number of trials (±S.E.M.) to reach the criteria of acquisition in the pre-shift and post-shift phases by each group. [a] Significant differences when compared to group 30-1/vehicle. [NS] Non-significant differences when compared to group 30-1/vehicle. [b] Significant differences when compared to group 1-1/vehicle. [ns] Non-significant differences when compared to group 1-1/vehicle).

Table 2
Effect of chlorpromazine

Group	Pre-shift phase	Post-shift phase
30-1/vehicle	9.5 (1.2) ^{ns}	22.4 (7.3) ^{b}
1-1/vehicle	11.6 (1.1) ^{NS}	2.2 (0.9) ^{a}
30-1/chlorpromazine-0.5	7.9 (1.7) ^{NS}	15.5 (5.5) ^{NS}
30-1/chlorpromazine-1	9.0 (1.7) ^{NS}	20.5 (3.1) ^{NS}
30-1/chlorpromazine-2	12.6 (1.4) ^{NS}	46.2 (9.1) ^{a}
30-1/chlorpromazine-3	15.2 (3.0) ^{NS}	50.2 (10.1) ^{a}
30-30/chlorpromazine-3	11.2 (1.4) ^{ns}	4.4 (1.8) ^{ns}
1-1/chlorpromazine-3	48.5 (8.2) ^{b}	40.8 (9.8) ^{b}

Mean number of trials (±S.E.M.) to reach the criteria of acquisition in the pre-shift and post-shift phases by each group. [a] Significant differences when compared to group 30-1/vehicle. [NS] Non-significant differences when compared to group 30-1/vehicle. [b] Significant differences when compared to group 1-1/vehicle. [ns] Non-significant differences when compared to group 1-1/vehicle).

3.1.2. Effect of thiopental sodium

The mean number of trials needed to reach the pre- and post-shift criteria in groups 30-1/vehicle, 30-1/thiopental-1, 30-1/thiopental-2, 30-1/thiopental-5, 30-1/thiopental-10, 30-1/thiopental-15 and 30-1/thiopental-20 are shown in Table 1. There were no differences between the thiopental-treated and control groups for the pre-shift phase. For the post-shift phase, however, significant differences between groups were observed ($H(6) = 11.59$, $P < 0.07$), but only between group 30-1/vehicle and those groups receiving 5 ($U = 8$, $P < 0.002$) and 10 mg/kg thiopental ($U = 16.5$, $P < 0.02$). Only these two doses of thiopental abolished the negative contrast effect in a manner similar to that observed with diazepam. There were no significant differences in the post-shift results between groups 1-1/vehicle (no contrast situation) and 30-1/diazepam, 30-1/thiopental-5 or 30-1/thiopental-10 ($H(3) = 2.55$, n.s.).

To investigate the possible action of thiopental sodium on the one-way avoidance task, we compared the results in group 1-1/vehicle and group 1-1/thiopental-5, both of which were studied in a no contrast situation. There were no significant differences between the two groups in the pre-shift ($U = 37.5$, n.s.) or the post-shift phase ($U = 33.5$, n.s.). At a dose of 5 mg/kg, thiopental sodium effectively abolished the negative contrast effect, without affecting performance of the avoidance task itself.

3.2. Experiment 2

Overall analysis of the results showed statistically significant differences between groups in pre-shift, $H(7) = 22.96$, $P < 0.001$, and post-shift phases, $H(7) = 26.79$, $P < 0.0004$. The results are summarized in Table 2.

3.2.1. Effect of chlorpromazine

As in experiment 1, comparison of groups 30-1/vehicle and 1-1/vehicle demonstrated the presence of a negative contrast effect. Although there were no significant differences between these groups during the pre-shift phase ($U = 22.5$, n.s.), the groups clearly differed in the post-shift phase ($U = 5$, $P < 0.003$). Chlorpromazine at doses of 0.5 and 1 mg/kg had no significant effect in either phase in comparison with group 30-1/vehicle (control). These results show that chlorpromazine (0.5 and 1 mg/kg) did not affect the successive negative contrast effect in one-way avoidance learning.

The findings in animals injected with 2 or 3 mg/kg chlorpromazine demanded separate analysis. We found no significant differences when we compared the pre-shift results for groups 30-1/chlorpromazine-2 and 30-1/chlorpromazine-3 with group 30-1/vehicle (control). In the post-shift phase, both doses of chlorpromazine increased the number of trials needed to reach the post-shift criterion (eight consecutive avoidance responses, Table 2) ($U = 13$, $P < 0.04$ for group 30-1/chlorpromazine-2; $U = 12$, $P < 0.03$ for group 30-1/chlorpromazine-3). To further investigate why the effect of this drug was the opposite of the thiopental sodium or diazepam effect, we tested two additional groups treated with the dose of chlorpromazine (3 mg/kg) that had the greatest effect on contrast, as reported below.

When group 1-1/chlorpromazine was compared to group 1-1/vehicle, the number of trials to reach criterion was significantly greater in chlorpromazine-treated animals in both the acquisition ($U = 8$, $P < 0.01$) and maintenance phase ($U = 5$, $P < 0.03$). In contrast, performance by group 30-30/chlorpromazine-3 was similar to that of group 1-1/vehicle in both phases ($U = 26.5$, n.s., and $U = 24$, n.s.), but different from that of group 1-1/chlorpromazine-3 (acquisition phase $U = 7$, $P < 0.007$; maintenance phase $U = 6$, $P < 0.06$). These results suggest that chlorpromazine at a dose of 3 mg/kg affected the one-way avoidance task itself in a low reward situation (1 s in the safe compartment), but not when the larger reinforcer was provided (30 s).

4. Discussion

The results now obtained showed, firstly, that thiopental sodium, a barbiturate with GABAergic action, abolishes successive negative contrast in one-way avoidance, in a dose-dependent way (at 5 and 10 mg/kg, but not at 1, 2, 15 or 20 mg/kg), and in a manner similar to that reported for diazepam. Secondly, chlorpromazine, a neuroleptic that acts as an antagonist of dopamine D_2 receptors, did not abolish the contrast effect at a dose of 0.5 or 1 mg/kg, but at a dose of 2 or 3 mg/kg significantly increased the number of trials needed to satisfy the learning criterion during the post-shift phase (eight consecutive avoidance responses). In other words, at these doses chlorpromazine enhanced the contrast effect.

The results we obtained with thiopental sodium are similar to those of Flaherty and colleagues, who reported that amobarbital sodium abolishes the negative contrast found in a drinking task when the concentration of sucrose (32%) available to the rats was suddenly reduced (4%) (Flaherty and Driscoll, 1980; Flaherty et al., 1982). The dose dependence of the effect of amobarbital sodium was another similarity between these results and our present findings with thiopental sodium: the contrast effect was reduced only at intermediate doses (5 or 10 mg/kg), but not at lower (1 or 2 mg/kg) or higher doses (15 or 20 mg/kg). Our results also showed that the effect of thiopental sodium on contrast was identical to the effect we previously reported for diazepam (Morales et al., 1992). This was not surprising, as both substances modulate the $GABA_A$ receptor complex and potentiate gabaergic transmission, albeit through different mechanisms: diazepam interacts with benzodiazepine receptors bound to the receptor complex, whereas thiopental sodium binds the selective ionophore for the chloride ion (Macdonald and Olsen, 1994).

Taken together, our results support the pharmacological validity of successive negative contrast, as defined by the criteria of Treit (1985, 1991): the animal model we used was sensitive to the action of traditional anxiolytics, i.e., benzodiazepines and barbiturates. However, another study showed that negative contrast was insensitive to buspirone, an anxiolytic substance that is not related to the $GABA_A$ receptor system, but acts preferentially through $5\text{-}HT_{1A}$ receptors (Torres et al., 1995). This difference has also been noted in conflict models, which involve a different set of experimental situations, and are widely used in studies of the pharmacology of anxiety (Barrett and Gleeson, 1991).

Our results with chlorpromazine at doses of 0.5 or 1 mg/kg showed that this drug has no effect on successive negative contrast in one-way avoidance: the groups of rats that received these doses did not differ from the control group (30-1/vehicle). Moreover, neither dose appeared to have sedative effects on behavior, as we saw no signs of interference with acquisition of the avoidance response (pre-shift phase). These findings are consistent with other published results, although the contrast situations used were different. For example, chlorpromazine, unlike chlordiazepoxide, failed to modify the characteristics of negative contrast in an appetitive task (straight runway), although at doses of, for example, 5 mg/kg, it had a clear sedative effect on motor behavior (Rosen and Tessel, 1970). Similar results were described by Flaherty and colleagues, who found that haloperidol and chlorpromazine had no effect on the negative contrast effect they investigated (see above) (Flaherty et al., 1992).

On the other hand, the administration of 2 or 3 mg/kg chlorpromazine enhances negative contrast, the opposite of

the effect reported for diazepam: experimental subjects required a significantly greater number of trials to reach the learning criterion in the post-shift phase. In contrast, there were no significant differences between groups in the pre-shift phase, a finding that, in principle, rules out a possible sedative effect of chlorpromazine. The acquisition phase is very sensitive to the sedative action of drugs (Morales et al., 1992). Chlorpromazine may interfere with the subject's ability to acquire the avoidance response under certain experimental conditions, e.g., when a dose of 2 or 3 mg/kg is used, and when the safe time is 1 s during both pre-shift and post-shift (group 1-1/chlorpromazine-3), or during only the post-shift phase (groups 30-1/chlorpromazine-2 and 30-1/chlorpromazine-3). This effect is not manifested when doses of 0.5 or 1 mg/kg are used, or when time in the safe compartment is 30 s (group 30-30/chlorpromazine-3). It could be argued that chlorpromazine at a dose of 3 mg/kg had a sedative effect, which might have been manifested in group 30-1/chlorpromazine-3 during the post-shift phase, and might have accounted for the increase in the number of trials needed to acquire the avoidance response in this phase. But this delayed sedation is not a tenable argument, as there was no difference between group 30-30/chlorpromazine-3 and the control group (1-1/vehicle) during the acquisition or the maintenance phase. Our results also suggest that chlorpromazine affected the efficacy of time in the safe compartment as a reinforcer; this can be surmised from the fact that chlorpromazine at doses of 2 or 3 mg/kg interfered with performance of the avoidance response only in subjects exposed to low-magnitude reinforcement (1 s), regardless of whether they were in the contrast situation (groups 30-1/chlorpromazine-2 and 30-1/chlorpromazine-3) or not (group 1-1/chlorpromazine-3).

The explanation we offer above is based in part on the anhedonia hypothesis, according to which block of cerebral dopamine (by antagonist drugs, for example) interferes with the rewarding value of reinforcers and their ability to sustain an operant behavior, at doses that do not affect the subject's motor skills (Wise et al., 1978; Wise, 1982). The effect we report is probably due to the well-known relationship between the dopaminergic pathways – particularly the mesolimbic pathway – and processes of reinforcement (Fibiger and Phillips, 1988; Rolls, 1975). However, this explanation, although consistent with our results, is provisional; it should be recalled that the validity of the anhedonia hypothesis has been questioned by several authors (see, for example, Tombaugh et al., 1982 and Wirtshafter and Asin, 1985). In their analysis of the effects of haloperidol on negative contrast, Flaherty and colleagues (Flaherty et al., 1992) rejected this theoretical approach as an explanation for some of the effects on their dependent variable (reduced fluid intake in both shifted and unshifted groups), and offered an interpretation based on the sedative effects of this drug. In our experiments we found no evidence of sedation at the doses of chlorpromazine used (see above), as an increase in the number of trials needed to acquire the avoidance response was evident only in the groups of rats exposed to low-level reinforcement. It nonetheless seems likely that a relationship exists between cerebral dopamine, the pharmacological features of the dopaminergic system, and processes of reinforcement, not only in appetitive tasks but also in aversive tasks such as one-way avoidance (Beninger, 1989; McCullough et al., 1993; Salamone, 1994). However, the nature of the relationship between these factors and the effects of chlorpromazine reported above remains to be elucidated.

In summary, thiopental sodium and diazepam, but not chlorpromazine, abolish the successive negative contrast effect on one-way avoidance. This finding supports the pharmacological validity of successive negative contrast, which is shown here to be sensitive specifically to the action of anxiolytic substances. We conclude that this approach fulfils commonly accepted criteria for use in current research on the experimental pharmacology of anxiety (Treit, 1985, 1991).

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