Diazepam attenuates Successive Positive Contrast in One-Way Avoidance Learning*

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Resumen

El diazepan atenúa el efecto de contraste positivo sucesivo en el aprendizaje de evitación de un sentido. Se analiza la influencia del diazepan en el contraste positivo sucesivo durante el aprendizaje de la tarea de evitación de un sentido. Los resultados mostraron que cuando se inyectaba a los animales "vehículo", el incremento del tiempo en seguridad (de 1 a 30 seg en el grupo de contraste) durante el entrenamiento, generaba una mejora de la ejecución, que superaba la de los animales que recibían desde el principio sólo el reforzamiento mayor (30 seg) o el menor (1 seg). Cuando se inyectaba diacepam, ese efecto de contraste positivo se anulaba y la ejecución de los tres grupos (1-30, 1-1 y 30-30) era similar al final del entrenamiento. Los resultados muestran un claro efecto de contraste positivo y su atenuación por la acción del diazepan confirmando hallazgos previos sobre la influencia conjunta del miedo y la relajación en la adquisición y mantenimiento de la respuesta de evitación. A partir de la teoría emocional de los procesos oponentes, la interacción entre la fuerza motivacional del miedo y el valor de incentivo de la seguridad podría explicar los fenómenos de contraste positivo y negativo y su atenuación mediante ansiolíticos.
Palabras clave: diazepan, contraste positivo, aprendizaje de evitación.

Abstract

This study examined the influence of diazepam upon the successive positive contrast effect in one-way avoidance learning. The results showed that when injected with vehicle, a safety-time increment (from 1 to 30sec in the contrast group) during one-way avoidance learning led to a performance improvement, surpassing that of two control groups receiving the larger (30sec) or the lower (1sec) reward (safe time) from the beginning of training. However, when three similar groups were injected with diazepam, this contrast effect disappeared and learning was similar in all groups at the end of training. These results demonstrated a positive contrast effect in one-way avoidance learning and its attenuation by diazepam, bearing out previous findings about the joint influence of fear and relief upon acquisition and maintenance of the avoidance response. From an opponent process theory, the interaction between the motivational strength of fear and the incentive value of relief can explain not only positive and negative contrast effects, but also how anxiolytics attenuate both effects.
Key words: Diazepam, Positive contrast, Avoidance learning.

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In one-way avoidance learning, subjects are exposed to two markedly different compartments. In one, the danger compartment, they receive a warning signal followed by a 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.

It has been repeatedly shown that time in a safe place plays a crucial role in one way avoidance learning. Increasing the time spent in the safe compartment enhanced the learning of the avoidance response (Cándido, Maldonado, & Vila, 1989; Denny, 1971; Modaresi, 1975). Moreover, Cándido, Maldonado, Megías, & Catena (1992) found that a sudden reduction in safety time (from 30 sec., the large reward, to 1 sec., the small reward) during one-way avoidance training led to a successive negative contrast effect similar to that observed when the amount (Crespi, 1942), quality (Elliot, 1928) or duration (Weatherly, Melville, & Swindell, 1997) of an appetitive reinforcer is reduced in appetitive conditioning. These effects suggested that safe time can be functionally equivalent to appetitive reinforces, acting as an incentive for the avoidance response, and that both appetitive and aversive behavior, may be based on similar learning mechanisms (Dickinson, 1980; Toates, 1986; Cándido *et al.*, 1989).

The most enduring account of the negative contrast effect has been that the sudden reward reduction induces a negative emotional reaction -such as frustration or anxiety- responsible for the impaired performance (see, for example, Amsel, 1992, Flaherty, 1996). Evidence in support of the involvement of some form of stress or emotional response in negative contrast, both in appetitive and aversive tasks, includes pharmacological (Flaherty, Greenwood, Martin, & Leszczuk, 1998; Morales, Torres, Megías, Cándido, & Maldonado, 1992), endocrinological (Mitchel & Flaherty, 1998) and neuroanatomical studies (Leszczuk & Flaherty, 2000; Liao & Chuang, 2003).

Recently, Cándido, Maldonado, Rodríguez, & Morales (2002) found a positive contrast effect in one-way avoidance learning, similar to that also obtained in appetitive tasks (Mellgren, 1972). An increase of safe time from 1 second (small reward) to 30 seconds (large reward) led to an enhancement of the avoidance response, surpassing that of a group receiving always the large reward (30 sec) from the beginning of training. Such a positive contrast effect further demonstrates the reinforcing value of safety time. However, although negative contrast has been easily found in appetitive and aversive learning, the positive contrast effect has been always elusive, suggesting that the two are not symmetrical effects (Flaherty, 1996). In appetitive tasks it was necessary to increase the difficulty of the task (Mellgren, 1972), to shift the reward before the learning asymptote was reached (Mellgren, 1971), or to decrease before increasing the amount of the reward, in order to obtain a positive contrast effect (Maxwell, Calef, Murray, Shepard, & Norville, 1976). In the same way, Cándido *et al.* (2002) showed that it was necessary to change the learning parameters from the negative contrast effect in order to obtain the positive contrast one. Thus, they had to use a limited number of trials (6 trials) before the shift in the reward and a reduced intensity of the shock, in order to increase the difficulty of one-way avoidance acquisition and to get a reliable positive contrast effect.

Although it is difficult to maintain that an increase of reward value could give

rise to a negative emotional state such as anxiety or frustration (as assumed to explain the negative contrast effect), the effect of positive contrast has also been related to the emotional reactions taking place during one-way avoidance learning, i.e. fear and relief. Cándido *et al.* (2002) proposed that any change of safe time in one-way avoidance learning may have an emotional impact responsible for both positive and negative contrast effects, given the joint presence of fear and relief during training.

Therefore, the main aim of this work was twofold. The first was to replicate the positive contrast effect previously found in one-way avoidance training (Cándido *et al.*, 2002). The second and more important objective was to look for the influence of an anxiolytic drug (diazepam) on this effect, a substance that usually attenuates the negative contrast effect (Morales *et al.*, 1992; Torres *et al.*, 1995, 1996), in order to explore the possible implication of emotional reactions associated to the increase in reward value (Cándido *et al.*, 2002; see Flaherty, 1996, for a review). As stated above, it is difficult that an increase of reward elicits anxiety or frustration, being the main assumption explaining the negative contrast effect. Therefore, an anxiolytic drug should not have any influence upon the positive contrast one. However, if diazepam attenuates also this last effect, it would be necessary to look for a theory able to explain both the negative and contrast effects within the same framework, as we will try to do in the general discussion from an opponent processes view taking into account the emotional processes -fear and relief- taking place during avoidance learning, (see, Candido *et al.*, 2002).

METHOD

Subjects

76 female Wistar rats about 90 days of age at the start of the experiment, were housed at a constant temperature of 20°C with a 12-hour light/dark cycle with food and water ad libitum. Training took place in the light phase.

Apparatus

The one-way Letica avoidance chamber consisted of two equal compartments 27cm long x 25cm wide x 28cm high, made of Plexiglas. The compartments were separated by a 0.5cm-thick partition 25cm wide x 28cm high, with a square 9 x 9cm hole at floor level and a removable automatic gate to allow movement between compartments. Both compartments thus were identical, 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 2cm apart center to center, connected in series to a Letica LI-2900 module capable of delivering a 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, nontransparent white plastic carrying box 24cm long x 14cm wide x 19cm high was placed in the safe compartment in contact with the communication gate. 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 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.

Procedure

The animals were put into the box and were allowed 5 minutes 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 the trials began. These trials consisted of a warning signal followed after 5 sec by an shock of 0.5 mA. Both the warning signal and the shock were continued until the animal moved into the safe compartment or until 30 sec had passed. The gate between the two compartments was opened as soon as the warning signal sounded and closed when the rat entered the safe compartment. Once the safe time had been completed, the transportation box was lifted over the apparatus and the rat was returned into the danger compartment (the roof of this compartment was opened briefly and then closed); then the box was replaced in the safe compartment of the avoidance chamber. Returning the rats to the danger compartment took from 1 to 2 sec.

The rats were assigned to one of six groups described in Table 1. Half of them were injected with diazepam and the other half with vehicle. Three groups (30-30/V, 1-1/V and 1-30/V, where the numbers stand for the time in safety during the first and the second phase of training and V means the administration of the vehicle before training)

Table 1. Time spent in the safe and the danger compartments (before warning signal) by the six groups of this experiment.

GROUP	PRESHIFT PHASE			POSTSHIFT PHASE		
	SAFE	DANGER	ITI	SAFE	DANGER	ITI
1-1/ V (n=8)	1	15	16	1	15	16
1-30/ V (n=16)	1	15	16	30	15	45
30-30/ V (n=16)	30	15	45	30	15	45
1-1/ D (n=10)	1	15	16	1	15	16
1-30/ D (n=16)	1	15	16	30	15	45
30-30/ D (n=10)	30	15	45	30	15	45

Note: The numbers in each "Group" stand for the time spent in the safe compartment during each phase. D and V mean that the group was injected with diazepam or vehicle before training. ITI stand for the inter-trial interval of each group in each phase.

were used to demonstrate the positive contrast effect. The other three groups (30-30/D, 1-1/D and 1-30/D, where the numbers stand again for the time in safety during the first and the second phase of training and D means the administration of diazepam before training) were used to study the effect of this anxiolytic on both, the avoidance task itself and the positive contrast effect.

The length of time in the danger compartment before the onset of the warning signal was the same for all conditions (15 sec). However, each group was kept in the safe compartment for a different length of time during each phase of training as shown in Table 1, being the inter-trial interval (ITI) for each group the sum of the danger plus the safe time. The possible influence of ITI changes as a function of safe-time changes upon both the successive negative and positive contrast effect was addressed in previous research (Cándido *et al.*, 1992; Cándido *et al.*, 2002) showing that contrast effects were not due to ITI changes per se. Avoidance training took place in two phases: a pre-shift phase with 6 trials, and a post-shift phase with 9 trials. The rats in the experimental positive contrast groups, either injected with vehicle (1-30/V) or diazepam (1-30/D), were allowed to stay in the safe compartment for 1 sec (the low reward) in the pre-shift phase and then, changed to 30 sec (the large reward) for the post-shift phase. The rats in the control groups had always the same amount of time spent in the safe compartment during both the pre-shift and the post-shift phases. Two of them spent only 1 second (the low reward, 1-1/V and 1-1/D groups) and the other two 30 seconds (the largest one, 30-30/V and 30-30/D groups). An avoidance response was considered to have taken place when the animal moved into the safe compartment and the communication gate was closed within 5 sec after onset of the warning signal. All training took place in a unique continuous session always lasting for less than half an hour.

Dependent variable. The dependent variable was the latency of avoidance or escape responses in each trial, grouped into blocks of three trials for analyses.

Drugs. Diazepam (D) or vehicle (V) was injected 30 min before training. Diazepam at a dose of 1ml/Kg (kindly donated by Productos Roche, Spain) was suspended in a 1% Tween-80 (Sigma, Spain) saline solution (vehicle) and administered IP in a total injection volume of 10 ml/kg.

RESULTS

Figure 1 shows the mean group log latency for blocks of three trials. For the pre-shift phase, the figure shows the final performance level (pre-b2), given the higher variability and the absence of any between-groups significant differences in the first block (all means above 2), as expected. For the post-shift phase, the results were grouped into three blocks of three trials (pos-b1, pos-b2 and pos-b3).

Log latency scores grouped into four blocks of three trials each (the last one from the pre-shift phase and the three of the post-shift phase) were subjected to a 3x2x4 (Contrast x Diazepam x Blocks) ANOVA. The first factor (Contrast) included the three groups (30-30, 1-1 and 1-30) as a function of time spent in the safe compartment during both phases, looking for a positive contrast effect. The second factor (Diazepam) studied the effect of the groups injected with Diazepam or Vehicle. The third factor included

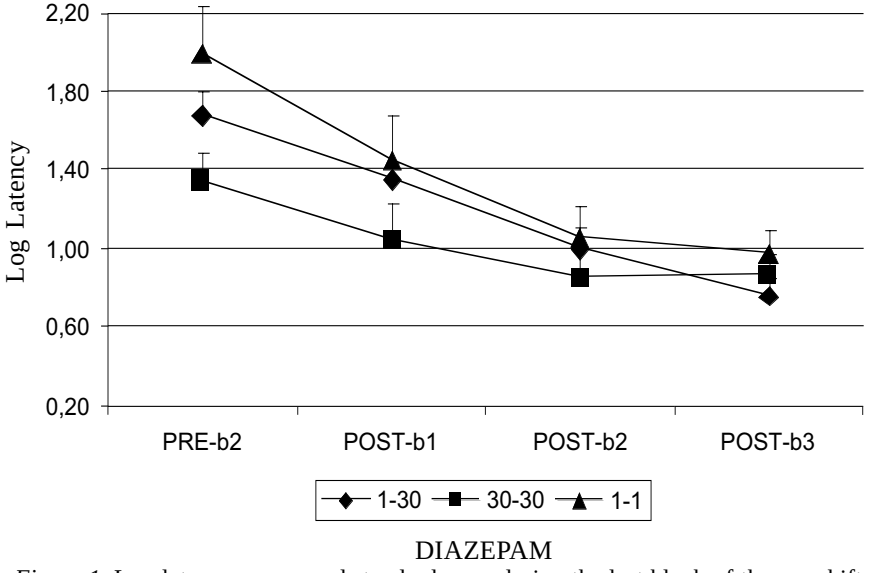

Figure 1. Log-latency means and standard error during the last block of the pre-shift phase and the three blocks of the post-shift phase of each of the groups injected with Diazepam. In each group, the numbers stand for the time spent in safety during the pre-shift and the post-shift phase respectively.

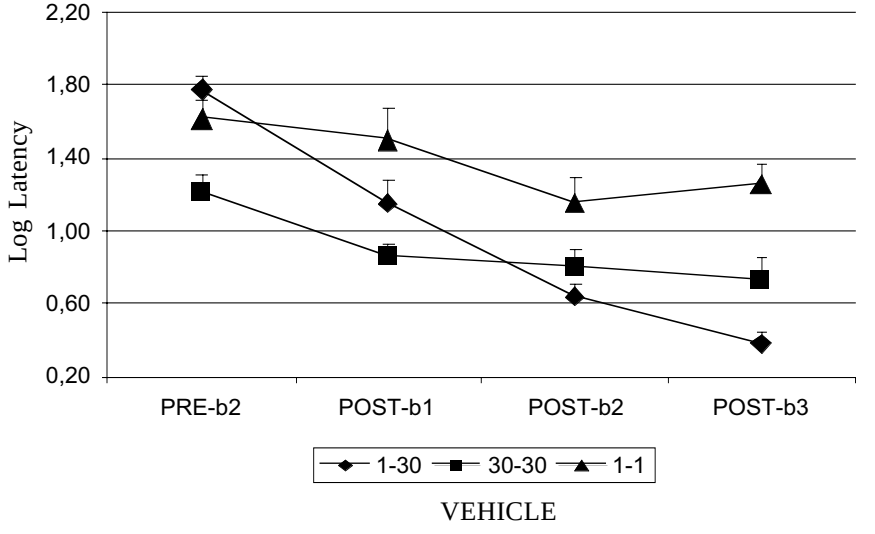

Figure 2. Log-latency means and standard error during the last block of the pre-shift phase and the three blocks of the post-shift phase of the three groups injected with Vehicle.

the four three trials Blocks. Statistical significance was set at $p < 0.05$ in all analyses and post-hoc tests. The results showed a significant effect of the three main factors, Contrast, [F (2, 70)= 18.82, MSE= 0.19], Diazepam, [F (1, 70)= 4.68, MSE= 0.19] and Blocks, [F (3, 210)= 52.79, MSE= 0.16]; but also of the third order interaction Contrast x Diazepam x Blocks, [F (6, 210)= 2,20, MSE= 0.16].

In the analysis of the interaction, we first analyzed the final performance of the pre-shift phase looking for the effect of safety time and the absence of influence of diazepan upon one-way avoidance learning. The unifactorial Anova of the last block of this phase (pre-b2, see figure 1) revealed significant differences among the six groups, [F (5, 70)= 5.45, MSE (Mean Square Error)= 0.19]. A posterior LSD test showed (Figure 1) that the two groups spending more time (30 sec) in the safe compartment significantly differed from the four groups spending only 1 second (except between 30-30/D and 1-1/V, whose differences were marginally significant $p < 0.06$). No differences were statistically significant either between the two groups spending 30 seconds or among the four groups spending only 1 second, as expected. These results confirmed once again that the more the time in the safe compartment, the easier the learning of the one-way avoidance response, being this effect independent of anxiolytics.

The most important results were obtained in the analysis of the third block of the post-shift phase looking for a positive contrast effect (Figure 2). The Anova revealed again a significant main effects of groups, [F (5, 70)= 7.71, MSE= 0.13], as in the preshift phase. However, the post-hoc LSD tests showed a very different pattern of between groups' differences. First of all, a clear positive contrast effect was shown, because the 1-30V group significantly differed from all the others 5 groups. This result means that the increase of safe time in this group led to the higher enhancement of performance during the second phase, being its latency lower compared to the latency of any other group. The differences obtained between the 1-30/V group, i.e. the positive contrast group, and the other two control groups 30-30/V and 1-1/V groups, all groups injected with vehicle, replicated the positive contrast effect previously found (Cándido *et al.*, 2002) and demonstrated the robustness of this effect. Most importantly, the significant differences between the two contrast groups (1-30/V and 1-30/D) as an effect of diazepam seem to prove that diazepam attenuates this positive contrast effect. In fact, this group did not differ from any other group except from the 1-1/V group in this block.

Finally, to further show the influence of diazepam either during the one-way avoidance task itself or in the positive contrast effect, we performed a 2x4 ANOVA for each pair of groups with the same training (the first factor being the injection or not of Diazepam and the second factor, the 4 Blocks of training under analysis). In the two pair of groups without any change of safe time during all training (30-30 and the 1-1), only the main effect of blocks was significant, [F (3, 72)= 7.33, MSE= 0.16] and [F (3, 48)= 8.21, MSE= 0.23] respectively. The absence of any significant effect of diazepam demonstrated once again that this drug has no effect upon one-way avoidance learning, as it has been shown in previous research. However, in the contrast (1-30) groups the 2x3 ANOVA, revealed not only a significant effect of Diazepam [F (1, 30)= 9.47, MSE= 0.16], and Blocks, [F (3, 90)= 67.14, MSE= 0.12], but also of its interaction, [F

(3, 90)= 3.02, MSE= 0.12]. A posteriori LSD tests showed no effect of diazepam during the first two blocks (i.e. the last block of the pre-shift phase and the first of the post-shift phase), but the latencies were significantly lower in the 1-30/V group than in the 1-30/D group in the last two block of the post-shift phase, [F (1, 30)= 7.60, MSE= 0.14] and [F (1, 30)= 11.77, MSE= 0.10], which demonstrated how diazepam attenuates the positive contrast effect showed by the 1-30/V group.

In summary, overall results bore out previous findings with regard to the influence of safe time on the acquisition of the one-way avoidance response (Cándido *et al.*, 1989) and the absence of significant effects of diazepam on one-way avoidance learning but not in the contrasts effects (Morales *et al.*, 1992, see also Gray, 1984).

Discussion

The main results of this research were firstly, the demonstration of a reliable positive contrast effect in one-way avoidance learning in the 1-30/V group and secondly, its attenuation by diazepam in the 1-30/D one. This last novel result however, need further research looking for its dose-dependency or the influence of other drugs, as it was made in the negative contrast effect (see Morales *et al.*, 1992; Torres *et al.*, 1995; 1996).

Overall results showed firstly, that the longer the time spent in the safe compartment (1 sec vs. 30 sec), the better the performance in one-way avoidance learning, as it happened in the pre-shift phase. Secondly, a sudden increase in safety time during avoidance training (from 1 sec to 30 sec) produced a successive positive contrast effect, as showed by the improvement of this contrast group compared with the 1-1 or 30-30 control groups. Finally, the injection of diazepam significantly attenuated the successive positive contrast effect previously described, although the drug did not affect the avoidance learning itself. These results are in accordance with previous research and emphasize once again the importance of safe time in one-way avoidance learning, suggesting that safe time act as a positive reinforcer of the avoidance response (Cándido *et al.*, 1992).

In order to jointly explain the positive and negative contrast effects found in one-way avoidance tasks, a recent paper (see Cándido *et al.*, 2002) offers a theoretical explanation based upon the opponent process model of habituation and conditioning (Solomon & Corbit, 1974; Schull, 1979), which makes also possible to understand its attenuation by diazepam. According to this view, the danger compartment may activate a negative emotional state (fear) due to the contingent relationship between the danger signal and the shock appearing in this compartment. Immediately after the performance of the avoidance response, a compensatory emotional process (relief) would be activated, staying active while the rat remains into the safe compartment. Accordingly, the avoidance response would be a mixture of flight from fear and approach to safety, being the weight of each emotional and motivational component of the avoidance response a function of the relative danger and safe time and of the homeostatic opponent processes (fear or relief) taking place in each compartment (Cándido *et al.*, 2002). Therefore, the positive and negative contrast effects may be due to changes in this process of “emotional

homeostasis" derived from the opponent process model of habituation and conditioning (Solomon & Corbit, 1974; Schull, 1979).

The negative contrast effect depends upon the reduction of reinforcement and almost all models agree that this reduction would produce an emotional response such as anxiety, frustration or disappointment, being the factor responsible of the response impairment (Gray, 1987; Flaherty, 1996). The pharmacological evidence that anxiolytics attenuates such an effect support the involvement of some form of stress or emotional response in negative contrast (Flaherty, Greenwood, Martin, & Leszczuk, 1998; Morales *et al.*, 1992). The theoretical proposal based upon the opponent processes previously outlined, can also be useful to better understand the successive negative contrast effect observed in one-way avoidance learning when safe time is reduced from 30 sec to 1 sec (Cándido *et al.*, 1992). In this case, the reduction in safe time would induce a decrease in relief and would also activate an aversive emotional state (frustration, anxiety, disappointment) that would be responsible for the inhibition of the approach response to the safe compartment and thus for the worsening in the avoidance performance. The attenuation of the negative contrast effect by an anxiolytic such as diazepam may be easily understood from this theoretical perspective, because the drug would reduce the aversive emotional reaction occurring when the safe time is shortened (Morales *et al.*, 1992). However, the successive positive contrast and its attenuation by injection of diazepam obtained in the present work seems to be more difficult to explain from a hypothesis based on an "anti-frustrative or anti-conflict" action of diazepam, given that an increase of safe time is supposed to induce a positive instead of a negative emotional reaction. However, the present results can be accommodated taking into account the same theoretical model based on opponent processes.

According to this view, as soon as the warning signal and the shock activating a fear response disappear, a compensatory emotional process (relief) may be activated and may remain active while the rat enters and stays into the safe compartment. In the pre-shift phase, the groups spending more time in the safe compartment, where the conditioned opponent state (relief) is in effect (30 sec), will learn more rapidly because of the higher incentive value of the safe place. By contrast, in the other groups that spent a very short time in this compartment (1 sec), as soon as the opponent process state would occur in the safe compartment, they are carried out into the danger place, reducing the relief and making the experimental situation more aversive. This shorter relief would be responsible for the inhibition of the approach response to the safe compartment and thus for the worsening in the avoidance performance, as it happens with the groups spending less time in the safe compartment. This lack of response would also increase the number and duration of the shocks received during this phase; thus fear of the danger compartment and the danger signal would be larger in these groups as compared to the group that was allowed to spend 30 sec in the safe compartment. When the time spent in safety suddenly changes from 1 to 30 sec, the reinforcing properties of the safe compartment would be expected to increase, because of the increase in the absolute duration of the safe time. In addition, given that fear to the warning signal is supposed to be greater during the pre-shift phase in 1-30 group as compared to the 30-30 control group, it could be assumed that the amount of the

opponent process state (relief) in the safe compartment during the second phase would also be larger in the contrast groups in comparison to the control group. These differences in the magnitude of activated opponent processes would explain the enhanced performance of the positive contrast group (1-30) in comparison to its control group (30-30). Therefore, this explanation assumes that the emotional response underlying both positive and negative contrast effects is also a function of both, the fear to the danger compartment and the relief experienced in the safe one. Given that anxiolytics attenuates the negative contrast effect probably due to the reduction of anxiety associated with the reward reduction (Morales *et al.*, 1992; Torres *et al.*, 1996), it was important to see whether these drugs could also influence the positive contrast effect and to look for an explanation of such effect.

It has been repeatedly shown that anxiolytics are able to reduce or abolish the aversive emotions that are activated in animal models of anxiety such as conflict, novelty, and frustrative non-reward tests (Arborelius & Nemeroff, 2002; Leslie, Shaw, McCabe, Reynolds, & Dawson, 2004). In this context, present data offer the possibility that diazepam could have reduced the negative emotional response (fear) in the danger compartment during the pre-shift phase. From the opponent processes theory previously described, this attenuating action on the fear component would indirectly affect the emotional impact of the reward change, and a blunted relief reaction would be observed in the contrast group injected with diazepam as compared to 1-30/V group. Although it could be supposed that an anti-fear action of diazepam should have affected the performance of the avoidance response in preshift phase, it has been repeatedly observed an absence of effect of benzodiazepines on the acquisition of one-way avoidance learning (Gray, 1977; Panksepp, Sacks, Crepeau, & Abbot, 1991), suggesting that the avoidance response may be controlled by additional mechanisms probably related with safety signals and relief (McAllister, McAllister, Scoles, & Hampton, 1986; Starr & Mineka, 1977). In any case, whether this emotional mechanism underlies the attenuating action of diazepam on successive positive contrast will be addressed in future research.

In summary, the present proposal assumes that the avoidance response would always be a mixture of flight from a dangerous place (motivated by the amount of fear) and approach to a safe one (motivated by the amount of relief). The specific weight of each component (flight or approach) would be dependent on the amount of activation of each emotional state (fear or relief) as a function of homeostatic opponent processes taking place in each compartment. Therefore, the reinforcing properties of the time spent in the safe compartment seem to depend not only on the relief achieved in the safe condition itself, but also on the intensity of the fear elicited by the danger signal. Positive and negative contrast effects would bring about new homeostatic emotional reactions which would influence the flight and approach components of the avoidance response. This hypothesis is consistent with the observed effects of anxiolytics, which would attenuate the emotional impact of safe time changes that improve (positive contrast) or interfere (negative contrast) the performance of the avoidance response. Finally, as explained before (Candido *et al.*, 2002), these results agree with and could clarify recent clinical findings on the importance of safety signals and context in the acquisition and maintenance of anxiety disorders such as agoraphobia. With Rachman

(1998), we proposed that anxiety disorders depend on the balance each patient achieves between signals of threat and signals of safety. Fear as well as anxiety generates escape and avoidance behaviors in their search for safety. This position seems similar to our proposal for explaining one-way avoidance learning and agrees with the fact that anxiolytics has a minor effect on "single phobias", once fear and safety is compensated. It is the change, the absence or the reduction of safety signals which led to anxiety, as it happens in agoraphobia or panic disorders, in which case, the effect of anxiolytics seems to be more effective, as it also happens in contrast effects.

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