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Effect of acute and chronic stress restraint on amphetamine-associated place preference: involvement of dopamine D_1 and D_2 receptors

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Abstract

The purpose of this study was to determine the D-amphetamine (1.0, 1.5 and 2 mg/kg i.p.)-induced place preference in rats pre-exposed to acute or chronic restraint stress, using the conditioned place preference model. We also studied the involvement of opioid and dopamine mechanisms in the acute restraint stress-induced increase of D-amphetamine-induced place preference. A single restraint session (2 h) but not chronic restraint (2 h/day for 7 days) leading to adaptation to the stressor, enhanced the D-amphetamine-induced place preference. This enhancing effect was prevented by haloperidol administration (0.4 mg/kg i.p.), (±)-sulpiride (60 mg/kg i.p.) or *R*(+)-SCH-23390 hydrochloride (*R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride, 30 μg/kg i.p.) 10–20 min prior to the acute restraint session. However, naltrexone pretreatment (1 or 2 mg/kg i.p.) failed to prevent the acute restraint-induced enhancement of D-amphetamine-induced place preference. These results suggest that: (1) the enhancement of D-amphetamine-induced place preference occurred after a single restraint stress but not following chronic restraint stress, (2) the stimulation of both dopamine D_1 and D_2 receptors is necessary for the development of single restraint stress-induced enhancement of D-amphetamine-induced place preference and (3) apparently, an opioid system is not involved in this acute restraint-induced effect.

Keywords: Restraint stress; Adaptation; D-Amphetamine; Conditioned place preference; Dopamine D_1 receptor; Dopamine D_2 receptor; Opioid system; Sensitization

1. Introduction

Stressful experiences have been shown to potentiate the psychomotor and/or rewarding effects of psychostimulants and related drugs (Antelman et al., 1980; MacLennan and Maier, 1983; Hahn et al., 1986; Leyton and Stewart, 1990; Piazza et al., 1990a; Kalivas and Stewart, 1991; Robinson and Berridge, 1993; Goeders and Guerin, 1994; Miczek and Mutschler, 1996). The interaction between stress and the pharmacological effects of psychostimulants has been proven to vary depending on the properties of the stressors, i.e., predictable vs. unpredictable (Goeders and Guerin, 1994), escapable vs. inescapable (MacLennan and Maier, 1983), the number of stress sessions as well as the type of stress applied (Herman et al., 1984; Hahn et al., 1986). Other factors such as chronic repeated exposure to stress, leading to adaptation to the aversive stimulus, have not been specifically examined in these studies. Furthermore, several chronic stress schedules were designed to minimize habituation to aversive stimulus, i.e., application of repeated stressors without a constant time interval between them (Herman et al., 1984), or using a type of stress such as social stress to which the animals do not readily adapt over the course of repeated social confrontations (Miczek and Mutschler, 1996).

It has been reported that repeated exposure to the same aversive stimulus induces several adaptive responses from monoamine sites in rats (Stone and Platt, 1982; Cabib et al., 1984; Kennett et al., 1985; Cancela and Molina, 1987; Cancela et al., 1988, 1990). These responses, which appear at a time when the animals have developed resistance to many of the adverse side-effects of stress, also influence the behavioral consequences of a subsequent exposure to a novel stressor. In this regard, it has been shown that a previous history of chronic stress, leading to adaptation,

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attenuates the behavioral suppression produced by acute stress in different tasks such as forced swimming, conflict and locomotor activity in a ''novel'' environment (Kennett et al., 1985; Cancela et al., 1991, 1995, 1996). There is evidence that the difference in behavioral response to the same stressful conditions could be a critical factor in predicting the probability of amphetamine self-administration (Piazza et al., 1989, 1990b). Since acute or chronic restraint modulates differently the behavioral response to a new aversive situation, it is possible that both treatments also modulate amphetamine's rewarding effects differently.

The mesolimbic dopamine system is known to play a critical role in the rewarding mechanisms of psychostimulants (Wise and Bozarth,1987; Di Chiara and Imperato, 1988; Koob, 1992), in the domain of the endogenous opioid system (Di Chiara and North, 1992). In addition, opioid peptides released in response to recurrent stress (Amir et al., 1980) seem to be involved in stress-induced changes in the dopaminergic neurotransmission underlying the sensitization process (Kalivas and Abhold, 1987). However, there is still no evidence of opioid involvement in restraint stress-induced changes in the reinforcement of D-amphetamine. As for D_1 and D_2 dopamine receptors, even though they are clearly involved in the sensitization induced by both psychostimulants and stress (Ujike et al., 1989; Vezina and Stewart, 1989; Kuribara and Uchihashi, 1993; Díaz-Otañez et al., 1997), restraint stress-induced effects on amphetamine-reinforcement have not been studied.

The conditioning place preference model has been used extensively to evaluate the neural and behavioral mechanisms of drug reinforcement (Spyraki et al., 1982; Mucha and Iversen, 1984; Shippenberg and Herz., 1987; Stinus et al., 1990). In the present study we used the procedure described by Stinus et al. (1990) which led to discarding of markedly ''biased'' animals. The aims of this study were to examine: (1) whether D-amphetamine-induced place preference developed similarly after a stress regime involving adaptive changes (i.e., chronic restraint), and after a stress regime which did not promote adaptive neural changes (i.e., acute restraint stress), (2) which dopamine receptor subtypes were predominantly involved in the restraint stress-induced increase of the D-amphetamine-induced place preference, (3) whether or not an opioid component might be critical for the development of such a restraint stress-induced effect.

2. Materials and methods

2.1. Animals

Adult male inbred Wistar rats (250–330 g) were used. The animals were maintained at 20–24°C under a 12-h light–dark cycle (lights on at 0700 h) with free access to food and water. The rats were housed six per box and placed in the experimental room for at least 7 days prior to trials.

2.2. Stress

The rats were immobilized daily for 2 h in a Plexiglass restraining device, for either one or seven consecutive sessions. The Plexiglass cylinders were devised so that the rats' tails emerged from the rear. All animals were stressed between 1000 and 1400 h. In order to maximize habituation to restraint stress, the interval between consecutive stress sessions was constant. The animals appeared healthy as evidenced by their coat texture and slight changes in body weight (Cancela et al., 1996).

All procedures were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals as approved by the Chemistry School, Cordoba National University Animal Care and Use Committee.

2.3. Place preference conditioning apparatus

Place preference conditioning was carried out using the apparatus and procedures described earlier by Stinus et al. (1990), with slight modifications. The device consisted of three rectangular boxes ($40 \times 33 \times 34$ cm) spaced at 120° from one another all within reach of a triangular middle area. The boxes were illuminated by a 15-W dark red light 1.0 m above them. Three distinctive sensory cues differentiated each compartment: the wall coloring (white, black dots or black stripes), the floor texture (stainless-steel grid closed, stainless-steel grid open or wooden floor), and odors (anise extract 2%, diluted acetic acid 2%, or nothing at all). Before the final design of the apparatus, we tested the three sensory cues independently of each other to obtain a balanced choice when all three sensory cues were combined. The final design was: (a) white, wooden floor, acetic acid; (b) stripes, stainless-steel grid open, anise extract; and (c) dots, stainless steel grid closed, and no smell. The mean time spent ($\pm$S.E.M.) in each compartment during preconditioning for the 302 rats selected for the experiments was: (a) 310.77 ± 12.14; (b) 283.77 ± 12.08 and (c) 308.45 ± 14.06 s.

2.4. General procedure

Experiments were all carried out from 0900 to 1700 h. The place preference conditioning schedule consisted of five phases.

2.5. Habituation

The habituation sessions were intended to reduce the novelty and stress associated with handling and injection procedures. All animals were handled twice daily for 2 consecutive days prior to the beginning of the preconditioning phase.

2.6. Preconditioning phase

The animals were placed in the middle triangular area and their location was recorded for subsequent 20 min. Animals showing strong unconditioned aversion to (less than 120 s of the session time) or preference for (more than 720 s) any compartment were discarded. For each rat, the two compartments with the most similar time allotments were chosen for conditioning. One was randomly paired to D-amphetamine and the other to isotonic saline vehicle. The unassigned compartment could be either the most or least preferred of the three. This procedure allowed a reduction of the imbalance in time spent in drug vs. vehicle paired compartments. The mean time spent in compartments to be paired with D-amphetamine was 266.4 $\pm$ 3.6 s, with vehicle it was 266.4 $\pm$ 3.6 s, and without treatment, 350.4 $\pm$ 3.6 s. Time spent in the middle area was 316.8 $\pm$ 6.0 s. Rats were assigned to one of the distinct groups consisting of 7 to 11 rats. The day after preconditioning, the rats were either immobilized for a single 2-h restraint period or for seven consecutive restraint sessions; the controls were left undisturbed in their home cages, as previously noted.

2.7. Conditioning phase

Twenty-four or forty-eight hours after the last restraint stress session, all animals were trained for place conditioning. This stage consisted of 1 conditioning day, which involved two trials of alternating D-amphetamine and vehicle administration. Doors matching the walls of the compartments allowed the confinement of the rats for 30 min right after drug administration. Experiments involved a single conditioning trial with amphetamine (0, 1, 1.5 or 2 mg/kg i.p.) in an attempt to assess the rewarding response to amphetamine at a near-threshold place preference. Such a manipulation was expected to enhance the difference in place preference conditioning scores between restraint stress and non-stress groups.

2.8. Testing

Twenty-four hours after conditioning, the test was carried out exactly as in the preconditioning phase (free access to each compartment for 20 min). Preference for the drug-paired compartment was expressed as the difference between the mean of the postconditioning and preconditioning scores.

2.9. Experimental design

2.9.1. Experiment 1

The influence of acute restraint vs. chronic restraint stress was evaluated on the D-amphetamine-induced place preference. The day after preconditioning, animals were randomly assigned to one of twelve conditions defined by treatment (0, 1 or 7 restraint sessions) and dose (0, 1.0, 1.5 and 2.0 mg/kg i.p.). Animals assigned to the non-stress group (0 restraint session) were left undisturbed in their home cages. During conditioning the rats were handled, weighed and given either saline or one of four doses of D-amphetamine (0, 1.0, 1.5, 2.0 mg/kg i.p.). Immediately after drug administration, each rat was confined to the selected compartment for 30 min. The order of drug and saline trials was balanced among subjects. Twenty-four hours after conditioning, all drug-free animals were tested in the same manner as during preconditioning.

2.9.2. Experiment 2

The place preference conditioning to D-amphetamine was evaluated on different days following the acute restraint stress. In this experiment conditioning was performed 24, 48 or 72 h following acute restraint. Animals were randomly assigned to one of six conditions defined by treatment (0 or 1 restraint stress session) and time (24, 48 and 72 h following restraint stress session). Since acute restraint stress enhanced the D-amphetamine-induced place preference at a dose of 1.5 mg/kg, this dose was selected for conditioning in this experiment. Twenty-four hours after conditioning (which was at 24, 48 or 72 h following restraint stress), the D-amphetamine-induced place preferences were tested.

2.9.3. Experiment 3

The influence of a mixed dopamine D_1/D_2 receptor antagonist on the acute restraint stress effect was studied in the D-amphetamine-induced place preference. Twenty-four hours after preconditioning, animals were randomly assigned to one of four conditions defined by treatment (0 or 1 restraint stress session) and drug: vehicle and haloperidol (0.4 mg/kg i.p.). Thus, four groups were formed. In the stress groups, the animals were weighed, and then injected with their corresponding drug, haloperidol (0.4 mg/kg i.p.) or vehicle, 30 min before immobilization. The non-stress groups were weighed, injected with their respective drug or vehicle, and returned to their home cages. Forty-eight hours after the stress event and/or drug injection, all animals were conditioned following a procedure identical to that reported for Experiment 1. The time delay between haloperidol administration and conditioning was essential to avoid a residue of drug in the blood during conditioning.

2.9.4. Experiment 4

The involvement of dopamine D_1 and D_2 receptors in the acute restraint stress effect in the D-amphetamine-induced place preference was examined. Rats were randomly assigned to any of the following experimental conditions: treatment (stress or no stress) and drug: (a) saline, (b) SCH-23390 and (c) sulpiride. The animals were injected with SCH-23390 (30 μg/kg i.p.), sulpiride (60 mg/kg i.p) or vehicle 15 or 20 min before restraint. The non-stress

groups were weighed, injected with their respective drug or vehicle, and returned to their home cages. Forty-eight hours after stress and/or drug administration, all rats were put through the conditioning trial.

2.9.5. Experiment 5

The involvement of an opioid mechanism in the restraint stress-induced effect in the D-amphetamine-induced place preference was examined. Animals were assigned to one of six conditions defined by treatment (0 or 1 restraint stress session) and dose (0, 1 or 2 mg/kg i.p. of naltrexone). Immobilization began 10 min after the injection. The non-stress groups were injected and left undisturbed in their home cages. Twenty-four hours after restraint and/or drug administration, all animals were submitted to the conditioning procedure.

2.9.6. Drugs

D-Amphetamine sulfate and naltrexone chloride were purchased from Sigma, St. Louis, MO, USA, haloperidol and L-sulpiride from Magel, Buenos Aires, Argentina, and *R*(+)-SCH-23390 hydrochloride (*R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride from Research Biochemical International, Natick, MA, USA. L-sulpiride and haloperidol were dissolved in a minimal volume of dilute acetic acid and then diluted with saline (0.9% w/v NaCl solution). The remaining drugs were dissolved in saline immediately before use.

2.9.7. Statistics

The data from Experiment 1 were analyzed with a two-way random effect model factorial analysis of variance (ANOVA), where the factors under consideration were treatment (0, 1 or 7 restraint stress sessions) and dose (D-amphetamine 0, 1.0, 1.5 or 2.0 mg/kg i.p.). Data from Experiment 2 were analyzed with a two-way ANOVA, where the factors were treatment (0 or 1 restraint stress session) and time (24, 48 or 72 h before the conditioning phase). Data from Experiment 3 were analyzed with a two-way ANOVA, where the factors were treatment and drug (haloperidol or saline). The data from Experiment 4 were processed with a two-way ANOVA, analysing treatment and drug (SCH-23390, sulpiride or saline). The data from Experiment 5 were analyzed with a two-way ANOVA, where the factors were treatment and dose (naltrexone: 0, 1 or 2 mg/kg i.p.). All ANOVAs were followed by a post-hoc Fisher test.

3. Results

3.1. Experiment 1

Fig. 1 shows the dose–response curves for the place preference elicited by D-amphetamine (0, 1.0, 1.5 or 2.0 mg/kg i.p.), in rats submitted to 0, 1 or 7 restraint sessions. Two-way ANOVA (treatment × dose) revealed a significant main effect of the treatment factor $F(2,100) = 6.00$, $P < 0.004$, as well as a significant effect of the dose factor $F(3,100) = 5.86$, $P < 0.002$. Furthermore, a significant interaction between treatment and dose $F(6,100) = 2.22$, $P < 0.05$ was observed. Fisher post-hoc comparisons revealed that only acute restraint stress induced a significantly higher place preference score at 1.5 mg/kg i.p. of D-amphetamine as compared with its respective non-stress control. Significant place preference values induced by D-amphetamine (2 mg/kg i.p) were obtained in the acute restraint stress group as well as the non-stress group. No difference was observed among place preferences following acute, chronic or non-restraint stress groups at 2 mg/kg of D-amphetamine. Fig. 1 also shows that neither acute nor chronic restraint stress affected the environmental preference/aversion per se.

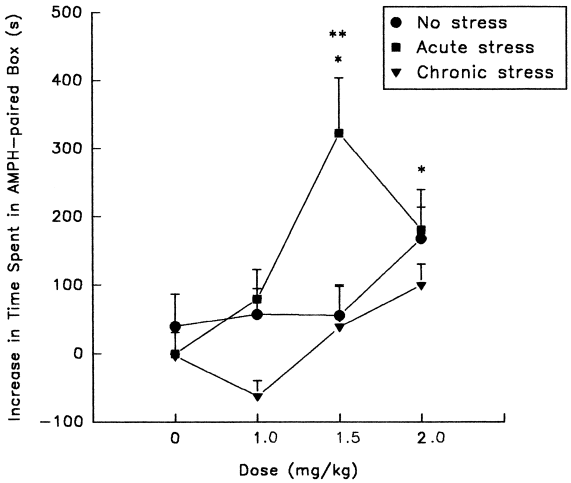

Fig. 1. Influence of acute and chronic restraint stress on the D-amphetamine-induced conditioned place preferences. The ordinate represents the difference in time spent for preconditioning and for postconditioning in the amphetamine-paired compartment. Thus, a positive value reflects a conditioned place preference. The abscissa represents the doses of D-amphetamine. All results are shown as means (±S.E.M.). * Significantly different from stress group given zero dose of D-amphetamine, $P < 0.02$. ** Significantly different from chronic stress and non-stress groups, $P < 0.001$.

3.2. Experiment 2

Fig. 2 shows the place preference conditioning promoted by D-amphetamine (1.5 mg/kg i.p.) in rats exposed to a single restraint stress session 24, 48 or 72 h before conditioning. Two-way ANOVA (treatment × conditioning day) revealed a significant main effect of the treatment factor $F(1,53) = 4.61$, $P < 0.04$, as well as a significant interaction between treatment and conditioning day $F(2,53) = 2.10$, $P < 0.005$. Post-hoc comparisons confirmed that a restraint stress session 24 or 48 h before conditioning with drug induced a significant increase in

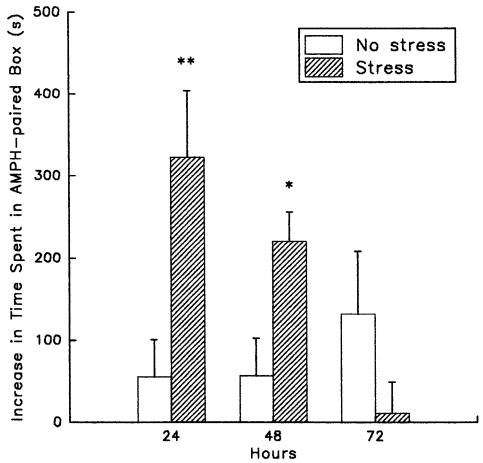

Fig. 2. Influence of acute and chronic restraint stress when administered 24, 48 or 72 h before the conditioning phase, on the D-amphetamine-induced conditioned place preferences. Values represent the means (±S.E.M.) of the difference between postconditioning and preconditioning scores for time spent in the D-amphetamine-paired compartment. * Significantly different from its respective non-stress and stress groups conditioned 72 h later, $P < 0.05$. ** Significantly different from its respective non-stress and stress groups conditioned 72 h later, $P < 0.002$.

the preference for the drug-paired side as compared with the other groups (the non-stress group and acute restraint stress group conditioned 72 h following stress session).

3.3. Experiment 3

Fig. 3 illustrates that haloperidol (0.4 mg/kg i.p.) pretreatment reversed the acute restraint-induced enhancement of the place preference produced by D-amphetamine. Two-way ANOVA revealed a significant effect of the treatment (stress and no stress) $F(1,33) = 7.45$, $P < 0.02$, as well as a main effect of drug factor (haloperidol or saline) $F(1,33) = 8.51$, $P < 0.01$. A significant interaction between treatment and drug $F(1,33) = 4.77$, $P < 0.04$ was observed. Post-hoc comparisons indicated that the acute restraint stress group injected with saline 30 min before immobilization displayed a greater preference response than the non-stress or haloperidol-stress groups.

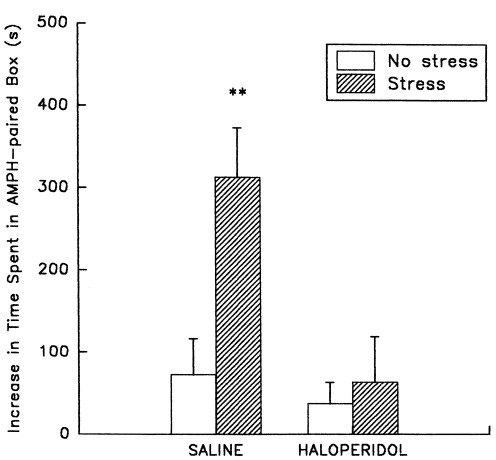

Fig. 3. Reversal by haloperidol of the restraint stress-induced sensitization to D-amphetamine. Rats were given haloperidol (0.4 mg/kg i.p.) or saline 30 min previous to the stress session. Values represent the means (±S.E.M.) of the difference between postconditioning and preconditioning scores for time spent in D-amphetamine-paired compartment. ** Significantly different from the non-stress and haloperidol-stress groups, $P < 0.003$.

3.4. Experiment 4

Fig. 4 shows that SCH-23390 (30 μg/kg i.p.) or sulpiride (60 mg/kg i.p.) pretreatment reversed the acute restraint-induced enhancement in the place preference induced by D-amphetamine. Two-way ANOVA (treatment × drug) indicated a significant effect of drug $F(2,48) = 3.22$, $P < 0.05$, as well as a significant interaction treatment × drug $F(2,48) = 4.16$, $P < 0.03$. Post-hoc Fisher test comparisons confirmed that the saline-restraint stress group was significantly different from the remaining stress and non-stress groups. Together, these results confirm that both D_1 and D_2 dopamine receptor antagonists totally impaired the enhancement in D-amphetamine-induced place preference following a single restraint stress session.

3.5. Experiment 5

Fig. 5 shows the influence of different doses of the opioid receptor antagonist, naltrexone (0, 1 or 2 mg/kg i.p.), on the acute restraint stress-induced effect on the place preference produced by D-amphetamine. Two-way ANOVA showed a main effect of the treatment factor (stress and no stress) $F(1,49) = 15.76$, $P < 0.003$. Post-hoc

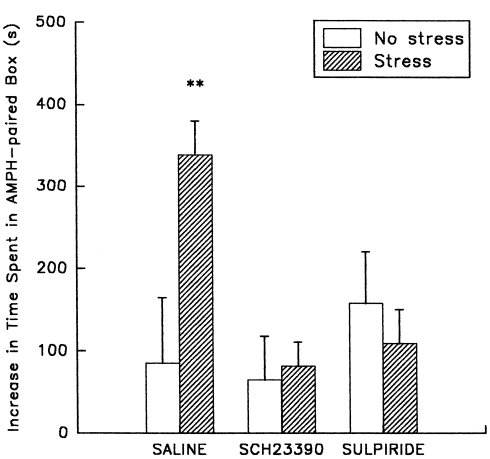

Fig. 4. Reversal by DA antagonist pretreatment of the restraint stress-induced sensitization to D-amphetamine. The animals were given SCH-23390 (30 μg/kg i.p.), sulpiride (60 mg/kg i.p.) or saline approximately 15–20 min previous to the restraint session. No-stress animals were injected in their home cages. Values represent the means (±S.E.M.) of the difference between postconditioning and preconditioning scores for time spent in the D-amphetamine-paired compartment. ** Significantly different from the remaining stress and non-stress groups, $P < 0.005$.

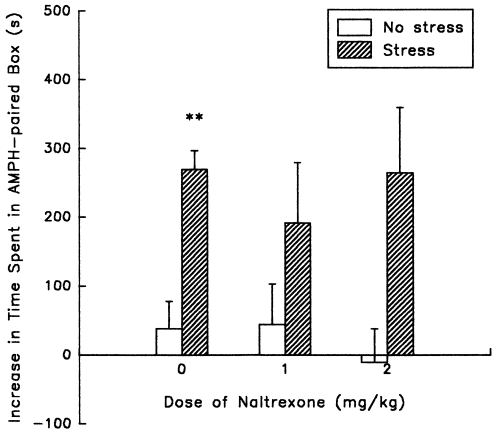

Fig. 5. Influence of naltrexone on the restraint stress-induced sensitization to D-amphetamine. Rats were given naltrexone (1 or 2 mg/ kg i.p.) or saline 10 min previous to the stress session. Values represent the means (±S.E.M.) of the difference between postconditioning and preconditioning scores for time spent in the D-amphetamine-paired compartment. ** Significantly different from the non-stress groups, $P < 0.03$.

comparisons showed that the saline-stress group was significantly different from the remaining non-restraint stress groups, but not from the naltrexone-stress groups. Namely, opioid antagonist administration failed to prevent the restraint stress-induced effect on D-amphetamine-associated place preference.

4. Discussion

The present study showed that prior exposure to a single restraint episode resulted in enhancement of the conditioned rewarding effect of D-amphetamine. Similar conditioning to D-amphetamine-induced reinforcing properties was displayed by the acute restraint stress and non-stress groups at a dose of 2 mg/kg i.p. of D-amphetamine (Fig. 1). However, only the acute restraint stress group showed a significant D-amphetamine-induced place preference at the intermediate dose of 1.5 mg/kg i.p. The increase in the conditioned reinforcing effects of a subtreshold dose of D-amphetamine (e.g., efficacy shift) might reflect a ''sensitization state'' to psychostimulants following acute restraint stress. The fact that D-amphetamine-induced place preference follows an inverted-U-shaped dose–response in the acute restraint stress group, would suggest that the lowest and the highest dose fix an infra- or supraoptimal stimulation to detect the highest sensitivity to the drug. This finding could be explained by the fact that the place preference conditioning to D-amphetamine appears to be ''all or none'' in nature, and as such, different from results obtained with amphetamine in self-administration models, where dose–response curves are typically observed (Glick et al., 1987). However, reports on self-administration also showed that individual differences among rats can be seen if low doses of amphetamine are used during the acquisition of self-administration (Piazza et al., 1989, 1990b).

Besides, the effect of acute restraint stress may resemble that described by Miczek and Mutschler (1996), who claimed that, after acquisition of cocaine self-administration, a social stress applied before sessions increased drug intake. This effect was described as activational, because the responses were increased in both the active and inactive manipulation. A previous study showed that only 0.5 mg/kg i.p. but not 0.75, 1 or 1.5 mg/kg i.p. led to restraint stress-induced sensitization on motor activity (Díaz-Otañez et al., 1997). In the present study, the challenge with D-amphetamine (1.5 mg/kg i.p.) during the drug conditioning phase did not enhance motor activity. It seems unlikely that a conditioned activational effect occurs during testing. Thus, different stimulation thresholds are necessary to verify stress-induced sensitization to D-amphetamine-induced motor activity or conditioning of drug reinforcement. The enhancement of the conditioned reinforcing effects of D-amphetamine lasted between 48 and 72 h. As previously shown, the restraint stress-induced sensitization of amphetamine-induced locomotor activity was more persistent (Díaz-Otañez et al., 1997). As for the reinforcing effect of D-amphetamine a single restraint could trigger a sensitized response but not one sustained throughout. The application of stressors at irregular intervals as well as the exposure to a variable chronic stress regime, would point to a long-lasting sensitization to amphetamine's rewarding effects. Preliminary evidence from our group seems to confirm the latter (data unpublished).

Place conditioning measures the association to an environment of a drug-induced affective state. This behavior may depend on the sensitivity of the individual to the drug-induced affective state. Acute restraint stress increased the conditioning to amphetamine rewarding properties, depending on the amount of time elapsed from stress to drug conditioning, i.e., an increase occurred 24 and 48 h but not 72 h following acute restraint stress (Fig. 2). On the contrary, prior exposure to chronic restraint stress did not induce such an increase (Fig. 1). Twenty-four or forty-eight hours following an acute restraint episode, a series of behavioral deficits as well as aversive motivational states was observed. Following chronic restraint stress, all these effects were reversed or inverted (Stone and Platt, 1982; Kennett et al., 1985; Murúa and Molina, 1990; Cancela et al., 1991, 1995, 1996). It is well known that this chronic restraint stress regime leads to the development of adaptive neural changes (Stone and Platt, 1982; Cabib et al., 1984; Cancela and Molina, 1987, Cancela et al., 1988, 1990). The onset of these adaptive changes temporally matches the disappearance of behavioral deficits and aversive motivational states induced by stress (Murúa and Molina, 1990; Cancela et al., 1991, 1995, 1996). The adaptive changes have been involved in the coping response to a new aversive event (Cancela et al., 1991, 1995). Interchangeable behavioral and neurochemical

events have been involved in the response to stress and amphetamines (Antelman et al., 1980; Cador et al., 1993). Apparently, these adaptive changes modulate the D-amphetamine rewarding effects following restraint. However, the lack of an enhanced preference response in chronic restraint could be, at least in part, attributed to an impairment of associative processes that establish the place preference response. Preliminary results showed that chronic restraint stress induced an opiate antagonist-associated place aversion similar to that observed following acute restraint stress (unpublished data). Thus, it seems unlikely that impairment of associative processes following chronic restraint stress could be responsible for its effects in the present study.

We observed that chronic restraint stress did not modify the response to D-amphetamine on reinforcement-related processes, even though it was previously shown that stress sensitized the response to D-amphetamine's locomotor activating effects (Díaz-Otañez et al., 1997). However, there is good evidence of the dissociability of these behavioral functions and their neural substrates (Robledo and Koob, 1993; Phillips et al., 1994a). Thus, distinct anatomical and functional properties have been attributed to the core and the shell of the nucleus accumbens as well as to other related neural structures (Deutch et al., 1993; Koob et al., 1993; Kalivas and Duffy, 1995). This might suggest that chronic restraint stress modulates differentially neural substrates underlying the sensitization to D-amphetamine-induced unconditioned (locomotor activity) or conditioned effects (reinforcing properties).

Our previous results with naltrexone and restraint stress pointed out the opioid–dopamine interaction in the development of restraint stress-induced sensitization to amphetamine locomotor activating effects (Díaz-Otañez et al., 1997). However, the opioid receptor antagonist did not affect the acute restraint-induced enhancement of the conditioned rewarding effects of D-amphetamine (Fig. 5). There is evidence that the locomotor assay is not generally related to a way of behavior directly accountable for reinforcement-related processes. Thus, the dopamine-dependent locomotor-stimulant properties of intra-ventral tegmental area infusions of opiates are associated with impaired conditioned reinforcer efficacy (Phillips et al., 1994b).

Our data showed that haloperidol, sulpiride and SCH23390 suppressed restraint effects on conditioned reinforcement to D-amphetamine (Figs. 3 and 4). Consistent with the present findings, we have previously shown that all the dopamine receptor antagonists used hindered the restraint stress-induced sensitization to D-amphetamine's locomotor activating effects (Díaz-Otañez et al., 1997).

An increase in response is not necessarily equivalent to sensitization processes in terms of the theory of Robinson and Berridge (1993). However, it is important to address the apparent similarity of underlying biological mechanisms for the sensitized response to D-amphetamine's locomotor activating and for rewarding properties following restraint stress. Thus, the present results help to identify the factors that contribute to boost the conditioned reinforcing properties of D-amphetamine as well as its possible mechanism. Further experiments should be carried out to elucidate this issue.

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