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European Journal of Pharmacology 299 (1996) 1-7

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An endogenous opiate mechanism seems to be involved in stress-induced anhedonia

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Received 20 April 1995; revised 30 October 1995; accepted 3 November 1995

Abstract

This study assessed the effect of an uncontrollable stressor on the preference for a palatable solution (sucrose 1%), and on the preference for a context associated with a single administration of D-amphetamine (3 mg/kg i.p.) by means of the conditioning place preference test. We also evaluated the effect of prior naloxone (2 mg/kg, i.p.) administration on the influence of this stressful stimulus in both tests. Animals previously submitted to a 120-min – but not 60-min – restraint period showed a selective reduction in the preference for sucrose intake as compared to unstressed animals. Similarly, an identical restraint exposure elicited a diminished preference for the place previously paired with amphetamine. Both stress-induced effects were blocked by prior naloxone administration. These data demonstrate that a highly aversive experience decreased the reinforcing efficacy of sucrose and amphetamine, suggesting that uncontrollable stress may lead to an impaired capacity to experience pleasure, which could resemble the anhedonia observed in clinical depression. Furthermore, an endogenous opiate mechanism activated by stress seems to be involved in stress-induced anhedonia since naloxone normalized the reduction of the rewarding induced by both reinforcers.

Keywords: Stress, uncontrollable; Naloxone; Anhedonia

1. Introduction

Exposure to inescapable and highly aversive experiences often leads to an increased passive behavior when stressed animals are subsequently exposed to novel stressors (Anisman et al., 1978; Katz et al., 1981; Murua and Molina, 1991; Molina et al., 1994). This altered behavioral response has been observed following either prior exposure to a variety of acute stressors or chronic aversive events (Katz et al., 1981; Weiss et al., 1981; Molina et al., 1994). For instance, rats exposed to acute stress or to a chronic variable stress regime display enhanced immobility during a subsequent forced swim experience, reduced locomotion in a novel environment (Weiss et al., 1981; Kennett et al., 1985; Plaznik et al., 1988; Cancela et al., 1991; Van Dijken et al., 1992), and altered escape performance (Katz et al., 1981; Murua et al., 1991; Molina et al., 1994). Most of these behavioral aberrations are normalized when stressed animals are given repeated antidepressant treatment (Katz et al., 1981; Murua et al., 1991), but not after the administration of other psychopharmacological agents. In addition, acute or chronic stress leads to a decreased sensitivity to reward (Willner et al., 1987; Plaznik et al., 1989) which could model anhedonia (reduced ability to experience pleasure), a core symptom of clinical depression. Furthermore, numerous reports have shown that repeated antidepressants antagonize stress-induced anhedonia (Zacharko et al., 1984; Plaznik et al., 1989). This body of evidence has led to the proposing of these stresses as valid animal models of depression (Willner, 1984, 1991).

According to results of numerous studies, several neurotransmitter systems seem to participate in the behavioral and neurochemical changes associated with uncontrollable stressful experiences (Weiss et al., 1981; Kennett et al., 1985; Molina et al., 1990; Edwards et al., 1992; Petty et al., 1994). Among these systems, an endogenous opiate mechanism activated in response to stress might be a potential mediator of this process. In fact, several findings have shown that stress-induced alterations were clearly attenuated in rats pretreated with an opiate antagonist

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SSDI 0014-2999(95)00754-7

(Hemingway and Reigle, 1987; Murua and Molina, 1990; Blustein et al., 1992; Molina et al., 1994).

The possibility of a functional role of endogenous opiates in these behavioral expressions is further supported by the fact that the release of endogenous opiates following stress exposure is a well established phenomenon (Amir et al., 1980; Kennett et al., 1985; Murua and Molina, 1991; Ruiz-Gayo et al., 1992). It is therefore reasonable to investigate whether activation of this endogenous mechanism could also be involved in other alterations evoked by aversive events. Several experimental designs have been developed to assess the reinforcing properties of various stimuli. Namely, sucrose or saccharin preference has frequently been used (Katz, 1982; Willner et al., 1987; Papp et al., 1991; Griffiths et al., 1992). Rats normally exhibit a high preference for palatable sweet solutions when these are paired with water, but this preference is significantly decreased either after acute exposure to a stressor of enough intensity or following chronic application of fairly mild or intense stressors (Katz, 1982; Willner et al., 1987; Willner, 1991). It is assumed that this change in preference represents an alteration in the ability to experience pleasure (Katz, 1982; Willner et al., 1987). Another design proposed to assess the rewarding efficacy of natural reinforcers or drugs such as amphetamine, is the conditioning place preference test. In this case, anhedonia is reflected by a reduced sensitivity to the reinforcing drug influence (Papp et al., 1991). By using both tests, it has been shown that repeated antidepressant administration reverses anhedonia induced by different stress schedules (Katz, 1982; Willner, 1991).

Considering that stress experience affects the organism's capacity to experience pleasure and that it could be a precipating factor in the onset of anhedonia, the goal of the present study was to investigate the role of an endogenous opiate mechanism in stress-induced anhedonia. Therefore, we evaluated the effect of naloxone and exposure to an uncontrollable stressor (restraint) on reward, using both preference for sucrose intake and place preference conditioning with amphetamine.

2. Materials and methods

2.1. Animals

Male Wistar rats (250–300 g) were used as experimental subjects. They were housed in groups of four or six in cages consisting of a plastic floor and walls and a wire-mesh top. Standard laboratory conditions with food ad libitum and a 12-h light-dark cycle (light on 7:00–19:00 h) were used.

2.2. Apparatus and procedure for sucrose preference

The animals were housed individually in cages made as above but with two 50-ml graduated tubes containing either 1.0% sucrose or tap water. The animals were allowed a week to adapt to drinking from these two calibrated tubes for only 3 h a day (13:00–16:00 h), with standard lab chow continuously available. This limited access to fluids has been used in prior studies and results in normal fluid intake (Zimmerberg and Brett, 1992). No fluid was available during the rest of the time. The drinking tubes were alternated daily to prevent the development of a positional habit. Further experimental manipulations and testing were started when the rats reached the criterion for sucrose preference. In our case, this criterion consisted of three consecutive days of sucrose preference exceeding 50% of total liquid intake following the training period. The majority of the rats tested usually showed a preference score between 80–90%. Twenty-four hours after they had reached the criterion for sucrose preference, 60 animals were subjected to 1.0- or 2.0-h restraint, or no stress. Immobilization was carried out in plastic restrainers, fitted closely to body size. In all cases, sucrose and water were available 1 h after the end of the stress, and the contents of the two bottles were measured after 3 h of intake.

Naloxone HCl (Sigma) was administered i.p. in a 2-mg/kg dose, prepared in distilled water (2 mg/ml), and injected 15 min prior to the immobilization session. Control rats were injected with distilled water, and both control and naloxone-treated animals received a volume of 2 ml/kg.

2.3. Apparatus and procedure for conditioned place preference

The place preference conditioning device consisted of a rectangular wooden chamber with three different compartments separated by removable guillotine doors. The two end compartments had dimensions 33 l × 25 w × 33 h, while the middle compartment was smaller and measured 13 l × 25 w × 25 h (all cm). One of the end compartments had white walls and a wire mesh floor. The other end compartment had black walls and a black rubber floor. The middle compartment had gray walls and was made of wood and had a smooth wooden floor. Both white and gray compartments were dimly lit, with no light in the black compartment.

In a pilot test we observed that rats exposed to this apparatus with free access to all compartments for 15 min spent slightly more time in the white compartment. In order to avoid possible criticism concerning the nature of the shift in the preference pattern following the pairing with amphetamine, we associated amphetamine injections with either the black or the white compartment. Thus, the possibility that the induced preference for the context associated with amphetamine was not due to a reduction in aversive properties of the less preferred side or to a neophobic effect could be eliminated. Therefore, approximately half the rats were conditioned in the black compartment and the other half were paired to the white compartment.

The procedure consisted of three daily phases during three consecutive days; on day 1: the pre-conditioning session, day 2: the conditioning session with amphetamine, and on day 3: the post-conditioning assessment. On day 1, all rats were placed in the middle compartment of the apparatus for 15 min with its doors removed. The total time spent in both the white and black compartments was recorded. On day 2, the animals were injected with amphetamine (3 mg/kg i.p.) or vehicle then immediately exposed for 20-min to one side of the apparatus; this was defined as the associated context. The conditioning session was performed from 16:00 to 18:00 h, and in order to balance the exposure to both sides, the rats were subjected to a prior 20-min exposure period (11:00–13:00 h) in the non-associated chamber. On day 3, the doors were removed and the rats were placed inside again. The time spent on each side of the apparatus was measured during a 15-min period, with no further drug administration. Preference was measured by comparing the time periods spent in the associated chamber during the pre-conditioning session and during the post-conditioning trial. Throughout the procedure, the apparatus was cleaned and swabbed with a dilute alcohol solution after each exposure. Seventy animals were randomly assigned to 8 experimental groups: vehicle-paired/vehicle-no stress; amphetamine-paired/vehicle-no stress; vehicle-paired/vehicle-stress; amphetamine-paired/vehicle-stress; vehicle-paired/naloxone-no stress; amphetamine-paired/naloxone-no stress; vehicle-paired/naloxone-stress; amphetamine-paired/naloxone-stress.

Immobilization was performed during a 2-h period which ended 1 h prior to the conditioning session. Naloxone (2 mg/kg, i.p.) administration was performed 15 min prior to the stress.

3. Results

3.1. Effects of different schedules of restraint on sucrose preference

Fig. 1 shows the effects of the different schedules of restraint on sucrose preference. As can be seen, rats exposed to a 2-h but not to a 1-h restraint period displayed a reduction in the percentage of sucrose consumption as compared to their respective pre-test scores. Further statistical analysis using a repeated measure analysis of variance (MANOVA) revealed a significant repeated measure effect [$F(1,21) = 4.71$; $P < 0.0416$]. The Newman-Keuls post-hoc test ($P < 0.01$) showed a significant difference between pre- and post-test sucrose percentages in rats submitted to 2-h immobilization.

3.2. Influence of naloxone pretreatment on the effect of restraint on sucrose intake

Similar scores for total fluid intake were observed following different treatments (means ± S.E.M. of total fluid intake; control: 21.1 ± 1.7 ml; stress: 22.5 ± 1.9 ml; naloxone: 21.5 ± 3.9; naloxone + stress: 19.7 ± 1.3 ml).

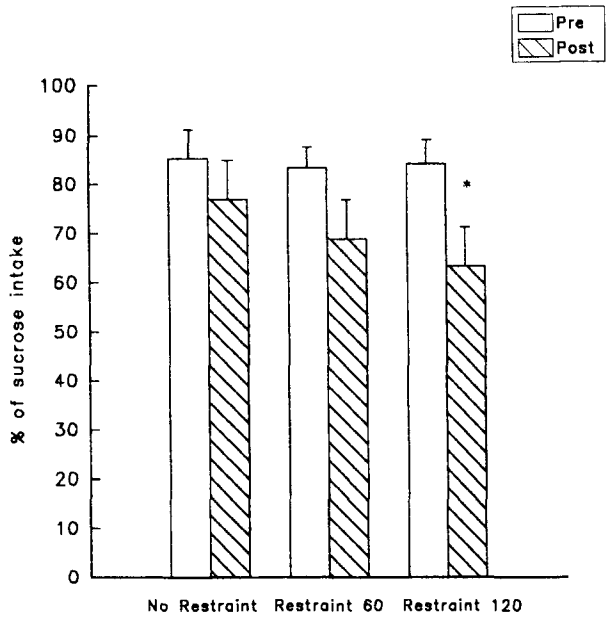

Fig. 1. Values represent the mean percentages of sucrose consumption over total liquid intake (±S.E.M.) in animals submitted or not to 60-min or 120-min restraint. $n = 8$. * Significant difference ($P < 0.01$) in the percentage sucrose intake between pre- and post-stress measure.

Fig. 2 depicts the effect of naloxone administration on the reduction in the sucrose preference induced by 2 h of restraint. As can be noted from this graph, rats exposed to the stress and injected with vehicle showed a decrease in sucrose intake; this effect was not evident in stressed animals given the opiate antagonist. Naloxone per se did not modify the sucrose preference. The MANOVA showed

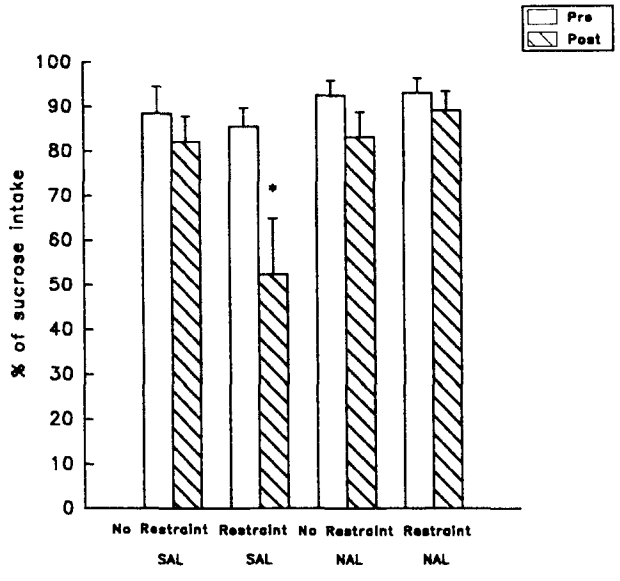

Fig. 2. Values represent the mean percentages of sucrose consumption over total liquid intake (±S.E.M.) in animals exposed or not to 120-min restraint session with previous vehicle (Vh) or naloxone (Nal) administration. $n = 8$–10. * Significant difference ($P < 0.01$) in the percentage sucrose intake between pre- and post-stress measure.

a repeated measure effect [$F(1,32) = 9.31$; $P < 0.0046$] and a significant interaction between stress and naloxone administration factors [$F(1,32) = 4.66$; $P < 0.0384$]. The Newman-Keuls post-hoc test ($P < 0.01$) revealed a significant difference between pre- and post-test percentage sucrose consumption in rats submitted to immobilization and injected with vehicle. No other significant differences or effects were noticed.

3.3. Effects of naloxone and restraint on amphetamine-induced conditioned place preference

Fig. 3 shows the conditioned place preference induced by one conditioning session with amphetamine. Rats injected with amphetamine showed an increase in post-conditioning preference as compared to the pre-conditioning score. This increase was not observed when the place was paired with vehicle. As can be observed, rats with stress paired with amphetamine did not show an increase in the time spent during the post-conditioning preference test as compared with the pre-conditioning scores when they were given vehicle. However, this effect was clearly evident in rats immobilized or not, and treated with naloxone. The MANOVA revealed a significant repeated measure effect [$F(1,62) = 9.84$; $P < 0.0026$]. A Newman-Keuls post-hoc test ($P < 0.01$) showed a significant difference between pre- and post-conditioning time spent in the amphetamine-associated context for both unstressed animals injected with vehicle and stressed or unstressed animals injected with naloxone. No other differences or effects were detected.

4. Discussion

In agreement with previous reports (Plaznik et al., 1989), the exposure to an uncontrollable stressor such as a restraint period of 120 min but not 60 min, significantly reduced the intake of a highly palatable solution (sucrose 1%). Stressed rats did not differ from unstressed rats in their total liquid intake (sucrose + water), suggesting that the influence of the aversive stimulation was selectively exerted on the preference for the sweet solution and was not the result of an unspecific reduction in liquid intake. The preference for sweet solutions following a stressful situation is produced irrespective of whether a nutritive or a non-nutritive solution is used (Katz, 1982; Willner et al., 1987). Therefore, and as previously suggested, the altered intake induced by stress is probably not caused by caloric differences, but reflects a decreased sensitivity to a natural reinforcer (Griffiths et al., 1992).

Besides, and in agreement with a wide number of studies (see Carr et al., 1989), the present experiments demonstrated that non-stressed animals exhibited an enhanced preference for the context associated with amphetamine. Similar to the effect of the stress on the preference for sucrose intake, exposure to a 2-h restraint period attenuated the preference for the side previously

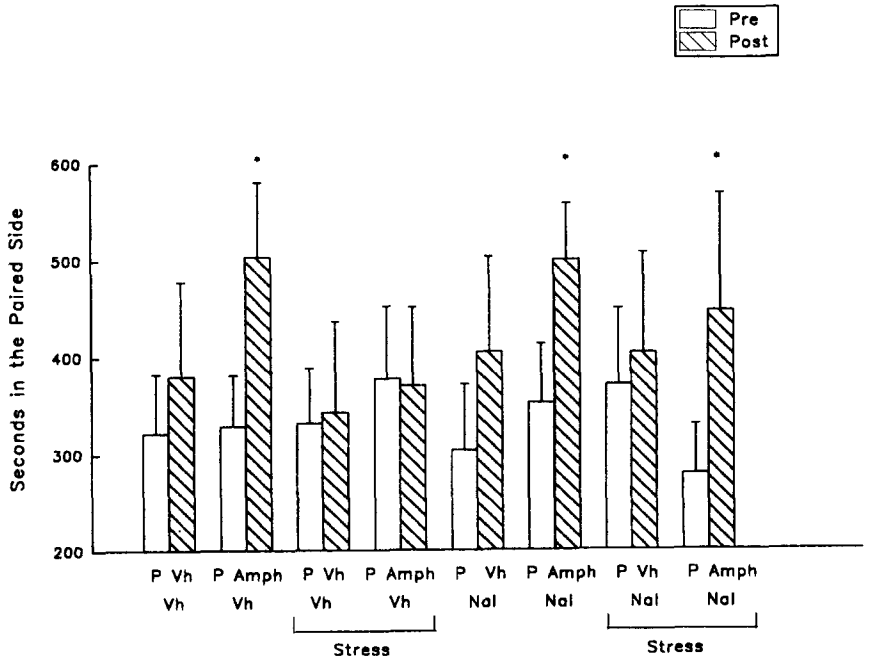

Fig. 3. Values represent the mean time (s ± S.E.M) spent in the paired side (vehicle paired: P Vh; amphetamine paired: P Amph) on day 1 (pre-conditioning: open columns) and on day 3 (post-conditioning: hatched columns). Prior to the conditioning session the rats were injected with vehicle (Vh) or naloxone (NAL) and subsequently exposed or not to stress. For details see Materials and methods. $n = 8–10$ rats per group. * Significant difference ($P < 0.01$) between pre- and post-conditioning measure.

paired with amphetamine, stressing the fact that this aversive situation also reduced sensitivity to amphetamine, a drug with well known reinforcing properties (Trujillo et al., 1991; Carr et al., 1989). The reducing effect of various stress schedules on the reward property of different reinforcers has been extensively studied (Katz, 1982; Willner et al., 1987; Papp et al., 1991; Zacharko and Anisman, 1991; Griffiths et al., 1992).

This evidence strongly supports the view that stress, including that of a long-term restraint session, reduced sensitivity to rewarding stimuli, an effect that could model the anhedonia observed in clinical depresssion. Further support for this notion is that prolonged antidepressant treatment normalizes the modification of reward processes induced by stress exposure (Katz, 1982; Zacharko et al., 1984; Willner, 1991).

Parallel to the influence on reward mechanisms, uncontrollable stressful events result in behavioral disturbances as assessed with a wide variety of models (see Willner, 1984). For instance, it was reported that exposure to a 2-h restraint session (the same stressor as that used in this study) induced clear hypolocomotion when these animals were subsequently placed in a novel environment (Kennett et al., 1985). Furthermore, increased time spent in immobility during a forced swim experience was observed following exposure to a similar stressor (Cancela et al., 1991). These, as well as other behavioral changes, have led to the suggestion that behavioral passivity may be considered a behavioral index of experimental depression, and a behavioral analogue of the psychomotor retardation symptom associated with human depression (Willner, 1991). The fact that behavioral aberrations provoked by uncontrollable restraint exposure are normalized by antidepressant treatment indicates that the behavior induced by long-term restraint events can be a valid tool for experimental depression studies (Kennett et al., 1985).

The attenuation or the reversal of behavioral deficits produced by uncontrollable stressors following opiate antagonists has been well documented (Hemingway and Reigle, 1987; Murua and Molina, 1990; Blustein et al., 1992; Molina et al., 1994). Thus, endogenous opioids seem to play a role in the modulation of these behavioral effects. Our observations showed that naloxone pretreatment normalized stress disturbances of subsequent rewarded behaviors, favouring the view that an endogenous opioid mechanism modulates the influence of stress exposure on rewarding stimuli.

Previous reports have shown that opiate antagonist administration can itself reduce different forms of carbohydrate intake (Rockwood and Reid, 1982; Islam et al., 1994) and produce place aversion (Carr et al., 1989; Trujillo et al., 1991). In addition, naloxone interferes with the rewarding and stimulating properties of amphetamine (Trujillo et al., 1991; Jones and Holtzman, 1994). It is important to point out that in most of these studies, naloxone was administered shortly prior to behavioral testing or amphetamine injection. However, in the present experiments, naloxone, with the dose and administration schedule used, did not influence sucrose intake in non-stressed animals, and was ineffective as a conditioning stimulus in the place preference test. Moreover, naloxone pretreatment of animals without stress did not affect the preference for the amphetamine-paired side. A probable explanation for these apparent discrepancies comes from the time lag between naloxone injection and the subsequent behavioral test. In the present study, naloxone was given 15 min before exposure to the 120-min restraint period, and behavioral testing and/or the conditioning trial were carried out 60 min following the conclusion of the stress experience. Since naloxone has a short plasma half-life in the rat – approximately 30 min – (Berkowitz et al., 1975; Misra et al., 1976), the lack of effect of naloxone pretreatment in non-stressed rats or in animals subsequently given amphetamine may be due to the prolonged time interval between the naloxone injection and the behavioral test or amphetamine administration.

Opiates also have rewarding properties, as measured in different behavioral models, including place preference conditioning (see Carr et al., 1989), self-administration (see Koob and Goeders, 1989), and the enhanced preference for the intake of palatable food or liquid (Czirr and Reid, 1986). In apparent contradiction with the rewarding property of opiates, the present observations showed that endogenous opioids are involved in stress-induced anhedonia. Besides, there is a recent report that the intraventricular administration of an enkephalin analogue immediately after an uncontrollable stressor reverses the changes in intracranial self-stimulation that had been induced by the aversive stimulus when the electrodes were placed on the dorsal A10 region, but not in other regions (Zacharko et al., 1990; Maddeaux and Zacharko, 1992). However, and in contrast to the reversal effect produced by antidepressants, the attenuation evoked by the enkephalin analogue was no longer evident when the animals were tested one week later (Maddeaux and Zacharko, 1992). The same authors described that intraventricular administration of the same opiate derivative prior to shock administration favored the decrease in self-stimulation from the ventral tegmental region (see Maddeaux and Zacharko, 1992), and suggested that excessive opioid stimulation may lead to even more profound behavioral aberrations. Therefore, we can tentatively suggest that a prolonged aversive experience, such as that used in the present study, could produce excessive opioid stimulation, which in turn may result in behavioral passivity and anhedonia. In addition, the endogenous opioid mechanism activated by stress could have different effects from those observed following exogenous opiate administration, depending on the neural substrate and/or the receptor subtype involved in each experimental trial. Alternatively, it could be argued that an endogenous opiate mechanism activated by stress could somehow alter the efficacy of different reinforcers, that could reflect the

reduced sensitivity observed in our experiments. Further experiments are necessary to elucidate this point.

Finally, and regardless of the precise mechanism involved, our evidence supports the notion that a major functional role of endogenous opioids is to modulate the behaviors adopted in response to stress. According to this view, opioids released by stress seem to be involved in the anhedonia induced by highly aversive experiences.

Acknowledgements

This work was supported by grants from CONICOR, SECyT and CONICET. The authors are grateful to Irma R. Medina and Gabriela Bazan for assistance with technical English.

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