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D_1 and D_2 Dopamine and Opiate Receptors are Involved in the Restraint Stress-Induced Sensitization to the Psychostimulant Effects of Amphetamine

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DÍAZ–OTAÑEZ, C. S., N. CAPRILES AND L. M. CANCELA. *D_1 and D_2 dopamine and opiate receptors are involved in the restraint stress-induced sensitization to the psychostimulant effects of amphetamine.* PHARMACOL BIOCHEM BEHAV **58**(1) 9–14, 1997.—The time course of the restraint stress-induced sensitization to the stimulant effects of amphetamine (AMPH, 0.5 mg/kg IP) on locomotor activity was investigated for up to 8 days. In a series of separate experiments, the involvement of opioid and dopaminergic mechanisms in the development of acute restraint stress-induced behavioral sensitization were characterized. Both a single restraint session (2 h) and chronic restraint (2 h per day for 7 days) similarly potentiated the effects of AMPH on motor activity. This behavioral sensitization was prevented by the administration of naltrexone (2 mg/kg IP), haloperidol (1 mg/kg IP), sulpiride (60 mg/kg IP) or SCH23390 (0.5 mg/kg IP) 10-20 min prior to restraint. These results indicate that 1) the development of sensitization to amphetamine-induced effects on motor activity does not depend on the length of exposure to stress (acute or chronic), 2) the stimulation of both D_1 and D_2 dopaminergic receptors is necessary for the development of the restraint stress-induced sensitization to AMPH and 3) an opioid system is also implicated in this sensitization process. © 1997 Elsevier Science Inc.

Restraint Adaptation Sensitization Stress Amphetamine Locomotor activity D_1 and D_2 dopamine receptors Opioid system

EITHER acute or repeated exposure to stress can potentiate the subsequent behavioral response to a single amphetamine administration (AMPH) (2,15,16,19,23,24,31,33,34). This process, called sensitization, may affect the interaction between stress and AMPH depending on the type of behavior being monitored and the stress regime applied. When AMPH-elicited motor activity or stereotypy is monitored, an intense degree of sensitization is evident following chronic stress (2,15, 16,19,23,24,34). This sensitization varies according to the number of stress sessions as well as the type of stress applied (15,16), whereas after the acute application of stress, the stimulant effects of AMPH on motor activity are not modified (15,16).

Other factors, such as chronic repeated exposure to stress, which can lead to an adaptation to the aversive stimulus (3,21,35,36,27,28), have not been specifically controlled in the studies of stress-induced sensitization to AMPH. It has been described that repeated exposure to the same aversive stimulus induces several adaptive responses on monoamine sites in rats (5,6,9,12,13,21,39). These responses, that appear at a time when the animals have developed resistance to many of the adverse consequences of stress, also influence the behavioral consequences provoked by a subsequent exposure to a novel stressor (8,10). In this regard, it has been shown that a previous history of chronic stress, leading to adaptation, attenuated the behavioral suppression produced by an acute stress in different tasks such as forced swimming, conflict and locomotor activity in a "novel" environment (8,10,11,19). Other studies have

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shown that the variability in the locomotor response to novelty is associated with the vulnerability to induce sensitization to AMPH (30,32). Also, a previous history of exposure to different stressors (i.e., inescapable or escapable footshock), has been demonstrated to be an important variable in the interaction of stress with the pharmacological effects of AMPH (24,29). Considering this evidence, it is possible that exposure to different schedules of restraint may differently modulate the development of sensitization to the stimulant effects of AMPH. Therefore, the purpose of this research was to determine if behavioral sensitization to the stimulant effects of AMPH develops and follows a similar time course after a stress regime which involves adaptive neural changes (i.e., chronic restraint), and a stress regime that does not involve adaptive neural changes (i.e., acute restraint). The behavioral sensitization induced by the repeated administration of AMPH and/or stress is generally associated with an enduring activation of mesocorticolimbic dopaminergic pathways (7,18, 19,20,39). There is also evidence for an opiate-dopamine cross sensitization in the nucleus accumbens after chronic treatment with morphine, enkephalin analogs or chronic footshock (19, 20,23). It is also well known that opioid peptides are released in response to recurrent stress (1), and the involvement of an endogenous opioid component in such stress-induced changes in dopaminergic neurotransmission has been suggested (18). However, no evidence of an opioid involvement in restraint stress-induced sensitization has been provided. Even though D_1 and D_2 dopaminergic receptors, have been reported to be distinctly involved in the sensitization induced by psychostimulants and chronic stress (4,22,37,38), such characterization has not been carried out in the case of sensitization induced by restraint stress. This study was therefore expanded to explore (i) which dopaminergic receptor subtypes are predominantly involved in the development of restraint stress -induced sensitization and (ii) whether or not an opioid component is also involved in restraint stress-induced sensitization to AMPH.

MATERIALS AND METHODS

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 07:00 h) with free access to food and water. The rats were housed six rats per box. They were placed in the experimental room for at least 7 days prior to the experiment.

Stress

Rats were immobilized daily for 2 h in a Plexiglas restraining device, for either one or seven consecutive sessions. The Plexiglas cylinders were designed such that the rats' tails protruded from the rear. All animals were stressed between 10:00 to 14:00 h. In order to maximize habituation to restraint, the interval between consecutive stress sessions was kept constant. Control rats were left undisturbed in their home cages.

Locomotor Activity

The testing apparatus used to measure locomotor activity consisted of a circular (60 cm diameter) cage equipped with two perpendicular infrared photocell beams located 3 cm above the floor. Interruption of either beam resulted in a photocell count. The testing apparatus was placed in a room different from the one where restraint was applied to control for possible conditioning effects. Animals were tested only once. All animals from control and experimental groups were tested between 10:00 and 16:00 h under white light in a quiet room. Animals were placed individually in the testing apparatus for a 1 h-habituation period. Animals were then injected with either saline (1 ml/kg IP) or AMPH (0.5 mg/kg IP), and motor activity counts were determined at 10 min intervals for 3 h following the injection. The dose of d-AMPH was chosen after a pilot study which pointed out that 0.5 mg/kg, but neither 0.75, 1 nor 1.5 mg/kg IP, allowed observation of the restraint stress-induced sensitization process.

PROCEDURE

Experiment I

Effects of acute and chronic repeated stress on the locomotor activating effects of AMPH were examined. Fifty-six rats were randomly assigned to one of six conditions defined by treatment (0, 1 or 7 restraint sessions) and drug: saline or AMPH. Twenty-four h after either acute stressor application or the last chronic stress session, rats were administered saline or AMPH and locomotor behavior was evaluated for 180 min following the injection.

Experiment II

The time course for acute and chronic restraint stress-induced sensitization to AMPH was examined. In Exp. I, it was shown that either acute or chronic restraint stress induced an increase of the AMPH locomotor activating effects 24 h following the last stress session. It was also observed that the response to saline was the same in all groups (control, acute or chronic restraint). Therefore, in this experiment, different groups of acute and chronically stressed rats were evaluated only for their reactivity to AMPH following one (acute) or seven (chronic) restraint stress sessions. Ninety-six rats were randomly assigned to one of 10 conditions defined by treatment (1 or 7 restraint sessions) and time (1, 2, 3, 4 or 8 days after one or seven restraint sessions). Thus, the reactivity to AMPH was determined at 24, 48, 72, 96 h or 8 days after acute or the last chronic stress session. The results obtained on the different days were compared between and within both groups. During this experiment, naive animals (not included within the group of ninety-six animals previously mentioned) were tested each week for their reactivity to AMPH, and it should be addressed that the reactivity to AMPH was the same as that observed in Exp.I (mean Exp. II = 198 ± 12, $n = 15$; mean Exp. I = 163 ± 32, $n = 13$). Naive animals were tested in an attempt to be sure that the lab conditions were kept constant.

Considering that the active period of the drug was 90 min, this time period was selected for the analysis of the results in Experiment I and II.

Experiment III

The effects of D_1 and D_2 receptor antagonist pretreatment on acute restraint stress-induced sensitization were examined. Sixty-two rats were randomly assigned to one of eight conditions defined by treatment (0 or 1 restraint stress session) and drug: vehicle (1 ml/kg IP), haloperidol (1 mg/kg IP), sulpiride (60 mg/kg IP) and SCH-23390 (0.5 mg/kg IP). Rats were immobilized 20 min after haloperidol administration, 5–10 min after sulpiride or SCH 23390 administration, and in the case of vehicle 10–15 min before stress. No-stress rats received drug

or vehicle and were returned to their home cages and left undisturbed. Twenty-four h after restraint and/or drug administration, all the animals were administered a challenge injection of AMPH.

Experiment IV

The influence of naltrexone pretreatment on restraint stress-induced sensitization to AMPH was examined. Forty rats were assigned to one of four conditions defined by treatment (0 or 1 restraint stress session) and drug, saline or naltrexone (2 mg/kg IP). Immobilization began 10 min after the injection. Control rats were injected and left undisturbed in their home cages. Twenty-four h after the restraint stress session and/or drug administration, all animals were evaluated for their reactivity to AMPH.

In Experiments III and IV, the photocell counts were analyzed during 180 min post-injection to show that antagonist pretreatment did not modify the duration of AMPH effect.

Drugs

D-AMPH sulfate and naltrexone chloride were purchased from Sigma Chemical Co., Saint Louis, MO, U.S.A., haloperidol and sulpiride from Magel S.A., Buenos Aires, Argentina, and SCH 23390 from Research Biochemical International, Natick, MA, U.S.A. l-sulpiride and haloperidol were dissolved in a minimal volume of diluted acetic acid and then diluted with saline (0.9 % w/v NaCl solution) for injection. The remaining drugs were dissolved in saline immediately before use.

Statistics

The data from Experiment I were analyzed by a two-way ANOVA, where the factors under consideration were treatment (0, 1 or 7 restraint stress sessions) and drug (saline or AMPH). Data obtained in Experiment II were analyzed by a two-way ANOVA, where the factors were treatment (1 or 7 restraint sessions) and days (1, 2, 3, 4 or 8 days). Data from Experiment III were analyzed by a three-way ANOVA for repeated measures, where the factors were treatment (0 or 1 restraint session), drug (vehicle, haloperidol, sulpiride or SCH 23390) and time as the repeated measure (10-min blocks during 180 min). The data of the Experiment IV, were analyzed by a three-way ANOVA where the factors were treatment (0 or 1 restraint session), drug (saline or naltrexone) and time (10-min blocks during 180 min). Fisher test for post-hoc individual comparisons was used with an alpha set at 0.05.

RESULTS

Experiment I

Figure 1 shows the cumulative total photocell counts over 90 min obtained after saline or AMPH injection in no stress and in both stressed groups 24 hr following restraint. A two-way ANOVA indicated a significant main effect of drug $F(1, 50) = 74.6$, $p < 0.001$ and treatment $F(2, 50) = 6.31$, $p < 0.004$ as well as a significant interaction between both factors, $F(2, 50) = 6.64$, $p < 0.003$. Post hoc comparisons indicated that neither acute nor chronic stress affected the locomotor response to saline, whereas both affected the response to AMPH. A similar increase in the reactivity to AMPH was observed between acute and chronically stressed animals with respect to that observed in no stress group.

Experiment II

Figure 2 shows the time course for the restraint stress-induced sensitization of the effects of AMPH 24, 48, 72, 96 h

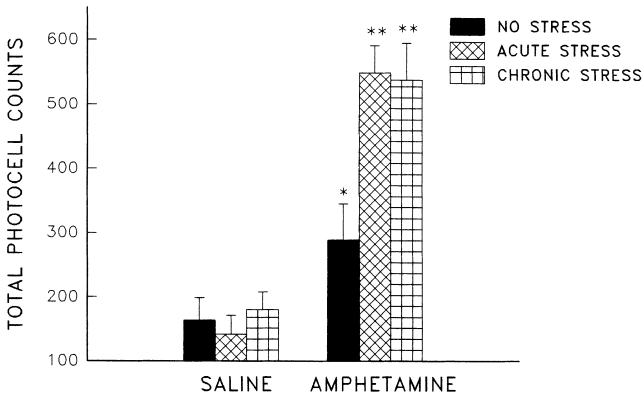

FIG. 1. Influence of acute and chronic restraint stress on the locomotor activating effects of AMPH. Rats were immobilized daily for 2 h for either one or seven consecutive sessions. Twenty-four h after either one (acute) or seven (chronic) restraint events, rats were placed in the testing apparatus for habituation during 1 hour; then, the locomotor response to AMPH (0.5 mg/kg IP) or saline was evaluated during 3 h. Values represent the mean (± S.E.M.) of total photocell counts over first 90 min, $n = 8$. *Significantly different from all groups administered with saline $p < 0.05$. **Significantly different from no stress group administered with saline and AMPH $p < 0.001$.

or 8 days after one (acute) or seven (chronic) stress sessions. A two-way ANOVA did not indicate any effect of treatment $F(1, 86) = 3.28$, $p < 0.07$ nor days $F(4, 86) = 0.92$, $p < 0.45$. In other words, no difference was observed in the reactivity to AMPH between acute and chronic restrained groups, after different days of one (acute) or seven (chronic) restraint sessions.

Experiment III

Figures 3A and B show the effects of dopaminergic antagonist pretreatment on acute restraint stress-induced sensitiza-

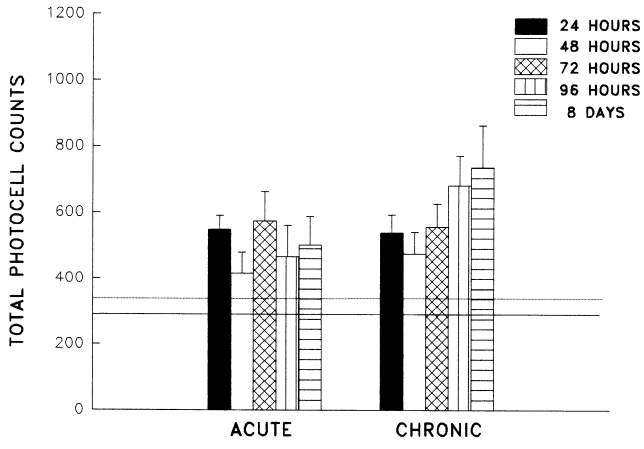

FIG. 2. Influence of acute or chronic restraint stress on locomotor reactivity to AMPH (0.5 mg/kg IP) at 24, 48, 72, 96 h and 8 days following the acute restraint or the seventh restraint stress session. Values represent the mean (± SEM) of the total photocell counts over the first 90 min, $n = 8$–11. The horizontal lines through the body of the graph represent mean (± S.E.M.) the activity level of naive animals not included in the statistical analysis.

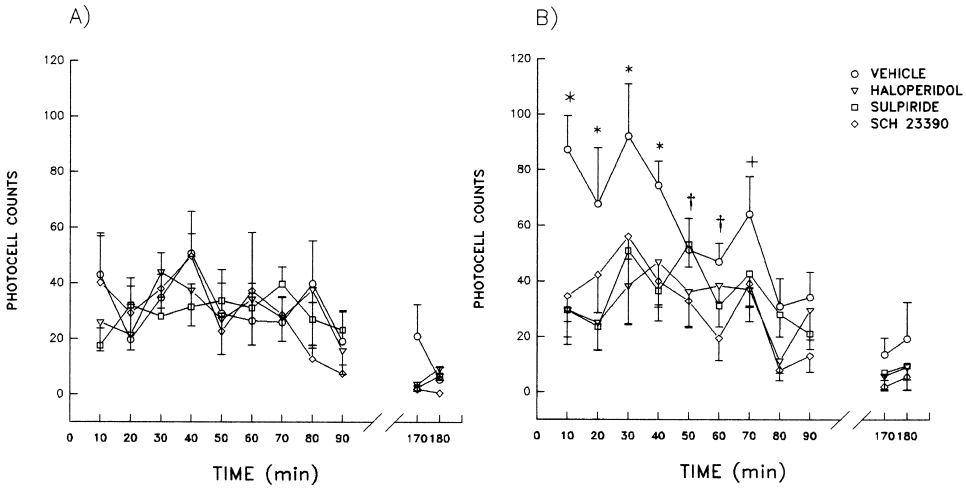

FIG. 3. Reversal by DA antagonist pretreatment of the restraint stress-induced sensitization to AMPH. A) No stress animals were injected with their respective drugs and placed in their home cages. B) Animals were administered with vehicle, haloperidol (1 mg/kg IP), sulpiride (60 mg/kg IP) or SCH 23390 (0.5 mg/kg IP) between 10–15 min previous to the stress session. Twenty-four h after restraint stress session and/or drug administration, the locomotor response to amphetamine (0.5 mg/kg IP) was evaluated. Values represent the means (± SEM) of photocell counts in 10-min periods during 180-min test, n = 7–9. * Significantly different from all the no stress groups and dopamine antagonist-stress groups $p < 0.01$. †Significantly different from SCH-23390-stress and SCH-23390-no stress groups $p < 0.05$. + Significantly different from haloperidol-stress, SCH-23390-stress, vehicle-no stress, haloperidol-no stress and SCH-23390-no stress groups $p < 0.01$.

tion to the locomotor activating effects of AMPH . When a three-way ANOVA was applied to these data, a significant effect of treatment $F(1, 54) = 5.11$, $p < 0.027$, drug $F(3, 54) = 8.38$, $p < 0.001$, time $F(17, 918) = 13.68$, $p < 0.001$ as well as a significant treatment x drug interaction $F(3, 54) = 2.87$, $p < 0.044$ was observed. Post-hoc comparisons indicated that photocell counts (10-min blocks) after restraint and vehicle administration were significantly higher at 10, 20, 30 and 40 min following AMPH administration, as compared to those of the remaining no stress and stress treated groups. At 70 min following AMPH injection, the vehicle-restraint stress group showed a significant increase of the locomotor response with regard to those observed in the no stress and stressed groups treated with haloperidol or SCH23390 (Fig. 3 A and B). Fig. 3A indicates that none of the drug pretreatments affected the reactivity to AMPH in non stressed animals.

Experiment IV

The effects of naltrexone pretreatment on restraint-induced sensitization to AMPH are displayed in Figure 4. A three-way ANOVA indicated a significant treatment effect $F(1, 36) = 7.34$, $p < 0.01$, drug $F(1, 36) = 4.06$, $p < 0.05$ and time $F(17, 612) = 8.16$, $p < 0.001$ as well as a significant treatment x drug x time interaction $F(17, 612) = 2.01$, $p < 0.01$. Post-hoc comparisons indicated that the naltrexone pretreatment abolished the restraint stress-induced increase of the photocell counts at 40 and 70 min after AMPH injection. After 10 min of AMPH injection, the vehicle- stress group showed a significant enhancement of the locomotor activating effect of AMPH with regard to the vehicle - no restraint stress and naltrexone - no restraint stress groups while the difference did not reach significance with respect to the naltrexone - restraint stress group. At only 60 min of AMPH injection, the naltrexone- restraint stress group showed scores significantly higher as compared to the remaining groups. A two-way ANOVA applied to the cumulative total counts during 180 min (data not shown) indicated a significant treatment effect $F(1, 36) = 9.94$, $p < 0.005$, a main effect of drug $F(1, 36) = 7.13$, $p < 0.01$ as well as a significant interaction between both factors $F(1, 36) = 10.32$, $p < 0.003$. Post- hoc comparisons of these cumulative data indicated that the restraint stress-induced increase on the locomotor activating effect of AMPH was completely abolished when animals were pretreated with naltrexone.

DISCUSSION

In agreement with other studies, our results indicate that both acute and chronic restraint stress enhance the stimulating effect of AMPH on motor activity (2,15,16,19,23,24,31,33,34). However, some of the previous studies reported that the effects of acute stress were either not observed or were lower than those evoked by the chronic exposure to stress (14–16). Also, those previous studies did not investigate the influence of chronic exposure to stress that not only leads to resistance to the adverse effects produced by this same stress (3,36), but also reverses the behavioral deficit elicited by a subsequent exposure to a novel stressful experience (10,21). Our results show a similar degree of enhancement in locomotor reactivity to AMPH following acute or chronic restraint stress at different days after stress. Several studies have found that seven restraint stress sessions (but not one or three) are the minimum necessary to produce adaptation to stress and tolerance to some of the behavioral and physiological consequences caused by acute stress (3,8,9,10,12,13,21). Therefore, the development of sensitization to AMPH does not seem to be associated with the stress regime applied, i.e., whether or not adaptation to

the aversive stimuli occurs. It has been recently described that a chronic variable stress procedure, which does not lead to behavioral adaptation, enhances the locomotor stimulating effect of low doses of morphine (25). Similarly, when a chronic restraint stress regime was designed to minimize habituation to restraint (i.e., applying the stress sessions at variable time intervals), a sensitization to the psychomotor effects of AMPH and morphine was found (14). Moreover, a progressive enhancement of the response to AMPH was seen after the last chronic footshock stress session with respect to the first one, in a schedule where stressors were daily applied without keeping constant the interval among them. In the present work, the similar degree of sensitization observed between the first and seventh stress session, could be attributed to the fact that this stress regime was designed to maximize adaptation. It has been shown that this stress schedule induces adaptive neural changes (9,12,13,21) and that some of these changes are opposite to or are not even present in those chronic stress regimes that do not lead to adaptation to the stressor (26). Thus, one could speculate that these adaptive neural changes could counteract the progressive increase in sensitization to AMPH previously reported. Further studies are necessary to clarify this point.

There is evidence showing that the difference in the behavioral response to the same aversive experience could be a critical factor in predicting the degree of sensitization to AMPH. Thus, rats which demonstrate a higher locomotor response to a novel environment are more likely to develop sensitization to chronic AMPH than rats with a lower reaction to the same stressor (32). Evidence from our lab and others indicate that previous exposure to acute or chronic stress induces different behavioral strategies in a subsequent and new aversive event (8,10,12). Twenty-four hr after exposure to acute restraint, we observed an anxiogenic effect in the light-dark transitions test (8), an increase in immobility time in the forced swimming test (9) and a decrease in exploratory activity in a "novel" environment (11). After chronic restraint, these effects were reversed or inverted when compared to acute restraint (8,10,21). Therefore, the adoption of distinct behaviors in response to an aversive situation would not always determine a difference in the development of restraint stress-induced sensitization to psychostimulants.

Imperato et al. (17) has found that restraint stress-induced increases in dopamine release may result in adaptation faster than that produced by the release from the aversive experience. Consequently, it could be hypothesized that the enhanced DA release in the nucleus accumbens, which is maintained at a high level from the first session of the stress regime throughout the repeated experiences, is responsible for the restraint stress-induced sensitization to the stimulant effects of AMPH. In addition to modifications of mesolimbic dopaminergic transmission (7,16,18,19,20,39), different neuropeptides including enkephalin are also known to be involved in stress induced sensitization (18). Our results with naltrexone and restraint stress support the involvement of opioid-dopamine interaction in the development of restraint stress-induced sensitization to AMPH. Our data also suggest that an opioid mechanism could also modulate the effects of restraint stress-induced effect on mesolimbic dopamine transmission underlying the behavioral response to AMPH. Also, the non-selective D_1 and D_2 antagonist haloperidol, the selective D_2 antagonist sulpiride and the selective D_1 antagonist SCH 23390 all supressed restraint stress-induced sensitization to AMPH.

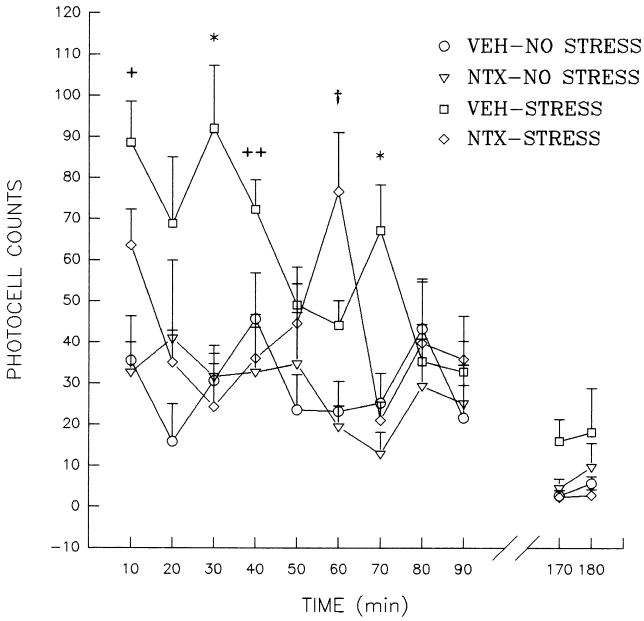

FIG. 4. Reversal by naltrexone of the restraint stress-induced sensitization to AMPH. Rats were administered with saline or naltrexone (2 mg/kg IP) 10 min previous to the stress session. Values represent the means (± SEM) of photocells counts in 10-min periods during 180 min, $n = 10$. + Significantly different from vehicle-no stress and naltrexone-no stress groups $p < 0.001$. ++ Significantly different from naltrexone-no stress and naltrexone-stress groups $p < 0.01$. * Significantly different from the remaining groups $p < 0.001$. † Significantly different from vehicle-stress, vehicle-no stress and naltrexone-no stress groups $p < 0.05$.

Almost the same suppressing effects on methamphetamine sensitization have been demonstrated with the combination of methamphetamine and haloperidol, sulpiride and SCH 23390, in terms of ambulatory activity in mice or locomotor activity in rats (22,37). The microinjection of the D_1 receptor antagonist, SCH-23390, into the A10/A9 region prior to peripheral administration of AMPH or morphine also prevented the development of behavioral sensitization to these drugs (19). In addition, a reduced D_2 receptor function after chronic treatment with psychostimulants or stress has also been previously proposed to explain electrophysiological and neurochemical changes after both treatments (19). The results obtained in the present work with dopamine receptor antagonists and restraint suggest that stimulation of both D_1 and D_2 receptors by stress-induced DA release is necessary for the development of sensitization.

In summary, our results confirm and extend the involvement of dopaminergic and opiate systems in the restraint stress-induced sensitization to AMPH and demonstrate that no difference could be observed in the restraint stress-induced sensitization following acute or chronic restraint.

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