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EFFECT OF ADRENALECTOMY AND CORTICOSTERONE  
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Effects of adrenalectomy (ADX) and corticosterone (CORT) on the development and expression of sensitization to the locomotor effect of cocaine (COC) were studied in rats. Sensitization was evoked by 5 daily injections of COC (10 mg/kg) and measured after a challenge dose of the drug (10 mg/kg) after a 5-day withdrawal (on day 10 of the experiment). ADX, performed before the start of COC administration, completely blocked the manifestation of COC-induced sensitization. In contrast, ADX performed on animals already sensitized to COC did not affect the sensitized locomotor activity response to a challenge dose of COC (on day 18). Pretreatment with CORT, 10 mg/kg, but not 5 mg/kg, before each of the 5 daily COC injections facilitated the development of COC sensitization, tested after a 5-day withdrawal. When pretreated with CORT alone (10 mg/kg), the challenge dose of COC administered on day 10 induced cross-sensitization to CORT. CORT (10 mg/kg) injected acutely before COC on day 10, potentiated the expression of COC sensitization. When given alone, on day 10 CORT (5–10 mg/kg) induced an increase in the locomotor activity of rats pretreated daily (5 injections) with COC. No drug treatment induced conditioned locomotion, as measured after saline challenge on day 8. Our results indicate that CORT facilitates the development and expression of COC sensitization, while ADX blocks the initiation of the behavioral phenomenon only. Moreover, there takes place cross-sensitization between CORT and COC, which indicates a close relationship between the drug-related mechanism and behavioral sensitization.

**Key words:** cocaine, adrenalectomy, corticosterone, sensitization, rats

## INTRODUCTION

Repeated exposure to psychostimulants (cocaine, amphetamine) induces the behavioral sensitization in rodents, which manifests itself as enhancement of various effects of these drugs such as, e.g. locomotor hyperactivity (1). This phenomenon is also observed in humans, being characteristic of psychostimulant psychosis (2, 3) vulnerability to drug abuse (4) and panic disorder (5).

Behavioral sensitization to psychostimulants depends on the mesolimbic dopaminergic transmission, as it is accompanied with an increase in extracellular dopamine concentration in this brain area (1, 6), and is suppressed by lesions (7) or pharmacological blockade (8, 9) of this transmission.

Numerous data indicate that behavioral sensitization to psychostimulants can also be evoked by repeated stress (6, 10, 11, 12, 13); moreover several lines of evidence show that stress-induced cross-sensitization to these drugs depends on glucocorticoid hormones: **1)** adrenalectomy (ADX) prevents the development of cocaine (COC) or amphetamine sensitization produced by repeated exposure to stress (10, 12, 14); **2)** a similar effect also occurs in animals treated with the inhibitor of the corticosterone synthesis metyrapone (13) or a corticotropin-releasing hormone antagonist (15); **3)** in stressed, ADX animals this sensitization is reinstated by administration of corticosterone (CORT) in doses restoring stress levels of the hormone (11, 12); **4)** mesolimbic dopaminergic neurones are provided with corticosteroid receptors (16) and glucocorticoids modify the activity of the mesolimbic dopaminergic system (17, 18); **5)** psychostimulants — like stress situations (19) — increase the secretion of glucocorticosteroids (20, 21).

At the same time — like in the stress-induced sensitization — CORT has been found to be involved in the sensitization to psychostimulants, evoked by treatment with the respective drugs. Actually, there are several reports on the role of this hormone in the sensitization produced by repeated treatment with amphetamine (22, 23, 24, 25), while only a few data refer to the participation of CORT in COC-induced behavioral sensitization (26, 27).

In the present study we examined the effect of CORT and ADX on the development and expression of COC-induced sensitization to its locomotor hyperactivity effect in rats. Moreover, CORT/COC and COC/CORT cross-sensitizations were also studied.

## MATERIALS AND METHODS

### *Animals*

The experiments were performed on male Wistar rats (280—300 g). The animals were housed in groups of four per cage at a room temperature of  $20 \pm 1^\circ\text{C}$  on a 12 h light/dark cycle (the light on 6.00—18.00 h). The rats had free access to food (Bacutil pellets) and water before the experiments, unless stated otherwise. All the experiments were carried out in compliance with the Polish Animal Protection Bill of April 21, 1997 and with the NIH Guide for the Care and Use of Laboratory Animals.

### *Drugs*

The following drugs were used (pre-session injection times given in parentheses): cocaine hydrochloride (COC, —5 min; Merck, Germany) and corticosterone (CORT, —65 min; Sigma

Chemical Co., USA). COC was diluted in saline (SAL) and injected i.p., while CORT was suspended in a 20%  $\beta$ -cyclodextrin (RBI, USA) and administered s.c. All the drugs were injected in a volume of 1 ml/kg.

### *Adrenalectomy (ADX)*

The animals were anaesthetized with a mixture of ketamine, 65 mg/kg (BioWet, Gorzów Poland), and xylazine, 15 mg/kg (ScanVet, Poland). Bilateral ADX was performed between 9.00 a.m. and 2 p.m. by exposing the kidneys and removing the adrenal glands. Sham-operated rats were submitted to the same surgical procedure except for the removal of the adrenal glands. To permit the rats to compensate for the salt loss caused by ADX, the animals were supplied with water containing 0.5% NaCl. After surgery, all animals were allowed a week to recover. The absence of the adrenal glands was verified by an ocular inspection after the experiment.

### *Locomotor activity measurements*

The locomotor activity of rats was recorded individually for each animal in Opto-Varimex cages (Columbus Instruments, USA), linked on-line to an IBM-PC compatible computer. Each cage (43x44 cm) was equipped with 15 infra-red emitters located on the *x* and *y* axes, and with an equivalent amount of receivers on the opposite walls of the cage. The behavior of rats was analyzed using Auto-track software (Columbus Instruments, USA). The locomotor activity was defined as a breakage of three consecutive photo-beams.

Before recording the locomotor activity, the animals were allowed a 60-min habituation period, after which they were taken out, injected with the drugs and placed back in the boxes. Locomotor activity was recorded for 60 min. Seven to eight animals per group were used.

### *Experimental design*

*Experiment 1.* During the first 5 days of the experiment, the animals received two injections, 60 min apart, of vehicle + SAL, vehicle + COC (10 mg/kg), CORT + SAL or CORT + COC (10 mg/kg). On day 8, the rats were challenged with SAL (a test for conditioned locomotion), and on day 10 with a challenge dose of COC (10 mg/kg; a test for the *development* of sensitization). Locomotor activity was recorded on days 1, 8 and 10.

*Experiment 2.* During the first 5 days of the experiment, the animals received two injections, 60 min apart, of vehicle + SAL or vehicle + COC (10 mg/kg). On day 8, the rats were challenged with SAL (a test for conditioned locomotion), and on day 10 the animals were challenged with: (A) vehicle + COC (10 mg/kg) or CORT + COC (10 mg/kg); a test for the *expression* of sensitization); (B) CORT + SAL (a test for *cross-sensitization*). Locomotor activity was recorded on days 1, 8 and 10.

*Experiment 3.* The rats were divided into one sham (SHAM)-operated group and one group subjected to ADX. During the first 5 days of the experiment, half of the animals in each group received SAL or COC (10 mg/kg). On day 8, the rats were challenged with SAL (a test for conditioned locomotion), and on day 10 with a challenge dose of COC (10 mg/kg; a test for the influence of ADX on the *development* of sensitization). Locomotor activity was recorded on days 1, 8 and 10.

*Experiment 4.* During the first 5 days of the experiment, the animals received COC (10 mg/kg). On day 8, the rats were challenged with SAL (a test for conditioned locomotion), and on day 10 with COC (10 mg/kg; a test for the *expression* of sensitization). On day 11, the rats sensitized to COC were subjected to surgery: half of them were SHAM-operated, the rest subjected to ADX. All the animals were left until day 18 (during that period no COC injections were given). On day 18, the animals were challenged with COC (10 mg/kg; a test for the influence of *post-conditioning* ADX on the *expression* of sensitization). Locomotor activity was recorded on days 1, 8, 10 and 18.

## Statistics

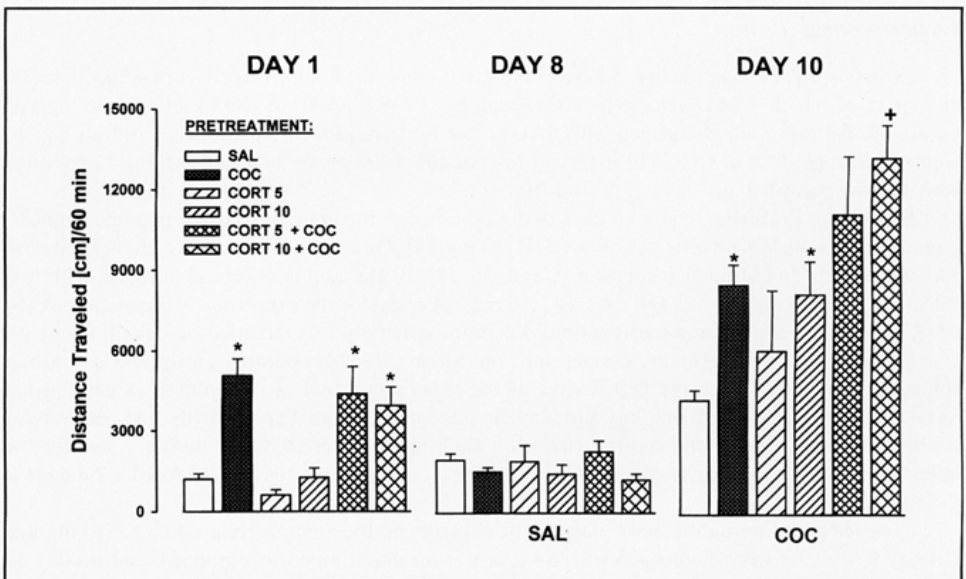
To evaluate the expression of behavioral sensitization, the response to COC (day 10) was compared with the response to its first injection (day 1) in the same animal, or with the response to the test drug injection (day 8) in animals treated with repeated SAL injections, using a paired Student's *t*-test or ANOVA, respectively. ANOVA, followed by *post hoc* Duncan's test, was performed to evaluate the treatment group effect.

## RESULTS

### Experiment 1.

Administration of a single dose of COC (10 mg/kg) to rats induced a four-fold increase in locomotor activity (*Fig. 1*; day 1). Two different doses of CORT (5 and 10 mg/kg) affected neither the basal nor the COC-induced locomotor activities of the animals (*Fig. 1*, day 1). Repeated (5 days) treatment with CORT (5–10 mg/kg) did not change the locomotor activity of rats (data not shown).

Pairing SAL injection with the experimental environment (cages) of COC sensitization did not affect the locomotor activities in any group tested (*Fig. 1*; day 8).



*Fig. 1.* Effects of CORT on the development of COC sensitization. COC (10 mg/kg) and/or CORT (5 and 10 mg/kg) were injected to rats daily for 5 days; on day 8 the animals were challenged with SAL (a test for conditioned locomotion), and on day 10 they were given a challenge dose of COC (10 mg/kg). \* $p < 0.001$  vs corresponding controls; +  $p < 0.05$  vs COC-pretreated animals.

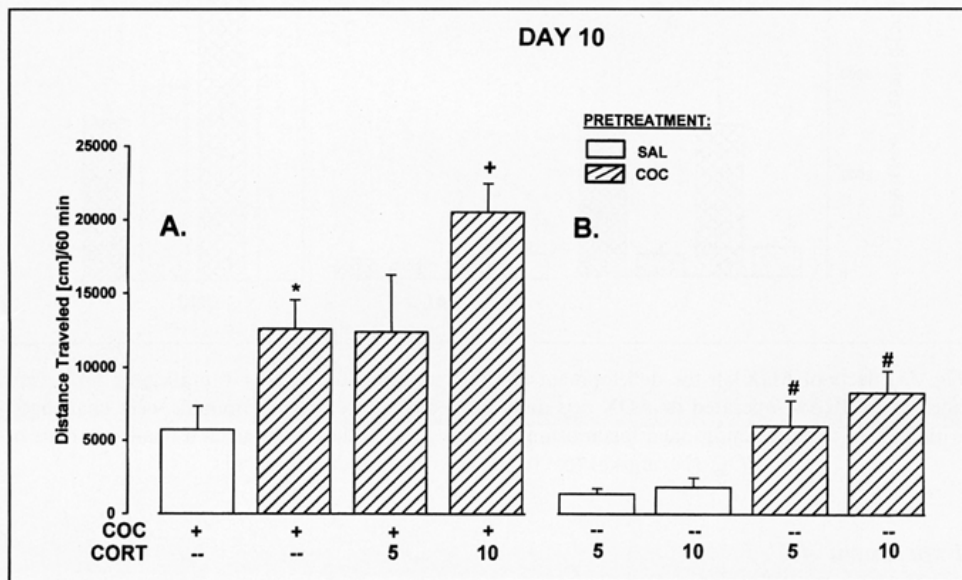
After 5 days of repeated COC (10 mg/kg) administration and after its 5-day withdrawal, a challenge dose of COC (10 mg/kg) induced marked behavioral sensitization observed as a ca. 60% increase in locomotor activity (*Fig. 1*, day 10). Pretreatment with 10 mg/kg, but not 5 mg/kg, of CORT before each of the 5 daily COC injections potentiated the development of COC sensitization, tested 5 days after withdrawal (*Fig. 1*, day 10). When pretreated with CORT alone (10 mg/kg, but not 5 mg/kg), a challenge dose of COC (10 mg/kg) induced cross-sensitization in rats on day 10, as the COC-evoked locomotor activity of that group was two times higher in comparison to the COC locomotion in rats treated with vehicle on days 1–5 (*Fig. 1*, day 10).

### Experiment 2.

CORT (10 mg/kg, but not 5 mg/kg), injected before COC on day 10, potentiated the *expression* of COC sensitization (*Fig. 2 A*); a 63% increase was observed after 10 mg/kg of CORT.

Given alone, on day 10 CORT (5–10 mg/kg) induced a significant increase in locomotor activity in animals pretreated with COC (10 mg/kg) on days 1–5 (*Fig. 2 B*).

No drug treatment induced conditioned locomotion, as tested after SAL challenge on day 8 (data not shown).



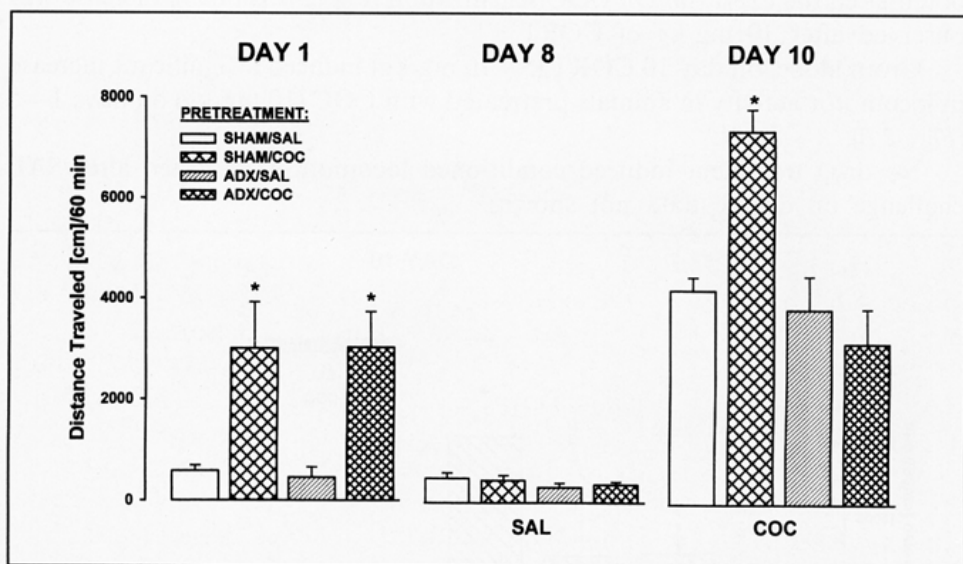
*Fig. 2.* Effects of CORT on the expression of COC sensitization. COC (10 mg/kg) or SAL were injected to rats daily for 5 days; on day 8 the animals were challenged with SAL (a test for conditioned locomotion), and on day 10 they were given either: (A) CORT (5–10 mg/kg) with a challenge dose of COC (10 mg/kg), or (B) CORT (5–10 mg/kg). \* $p < 0.01$ , # $p < 0.001$  vs corresponding controls; +  $p < 0.05$  vs COC-pretreated animals.

### Experiment No. 3.

As shown in *Fig. 3* (day 1), the locomotor activity of ADX animals did not differ from that of SHAM-operated controls after acute SAL injection. Acute COC treatment (day 1) induced approximately a 5-fold increase in locomotor activity in both SHAM-operated and ADX rats; that locomotor response did not differ between the two groups.

Neither ADX nor any drug treatment induced conditioned locomotion in rats, as observed after challenge with SAL (*Fig. 3*, day 8).

The COC (10 mg/kg)-induced locomotor activity was significantly enhanced in SHAM-operated rats after 5 daily injections of COC, followed by a 5-day of withdrawal period (*Fig. 3*, day 10). In contrast, such enhancement was not observed after a challenge dose of COC (10 mg/kg) in ADX animals.

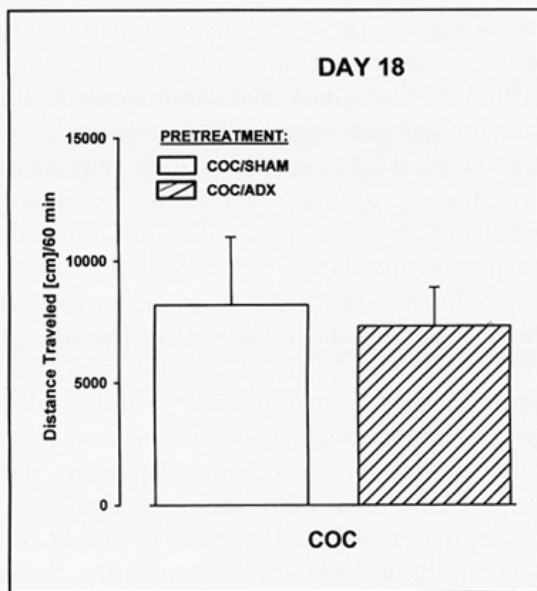


*Fig. 3.* Effects of ADX on the development of COC sensitization. COC (10 mg/kg) or SAL were injected to SHAM-operated or ADX rats daily for 5 days; on day 8 the animals were challenged with SAL (a test for conditioned locomotion), and on day 10 they were given a challenge dose of COC (10 mg/kg). \* $p < 0.001$  vs corresponding controls.

### Experiment 4.

As shown in *Fig. 4*, in animals already sensitized to COC (10 mg/kg) by its 5 daily injections, ADX did not affect the sensitized locomotor response to a challenge dose of COC (10 mg/kg) given 7 days postoperatively.

Fig. 4. Effects of post-conditioning ADX on the expression of COC sensitization. COC (10 mg/kg) was injected to rats daily for 5 days, on day 8 the animals were challenged with SAL (a test for conditioned locomotion) and on day 10 they were given a challenge dose of COC (10 mg/kg). The animals sensitized to COC underwent surgery: half of them were SHAM-operated, the other half were adrenalectomized. After recovery, the animals were challenged with COC (10 mg/kg).



## DISCUSSION

The results of the present study indicate that endogenous corticosteroids play a significant role in the development, but not expression, of COC-induced sensitization in rats. In fact, we demonstrated that ADX performed one week before the start of a 5 day-treatment with COC completely blocked the manifestation of the psychostimulant — induced sensitization, examined 5 days after the drug withdrawal. Accordingly, at that time (day 10 of experiment 3), in sham-operated animals a challenge dose of COC evoked locomotor hyperactivity which was ca. 75% stronger in the psychostimulant—treated than in SAL-receiving (days 1—5) rats, while no such difference between COC- and SAL-treated animals in their response to a challenge dose of the psychostimulant was observed after ADX (Fig. 3). On the other hand, no difference in the locomotor response to a challenge dose of COC was found between sham-operated and ADX animals (day 18 of experiment 4; Fig. 4) in which the surgery (sham and ADX) was performed on day 11, i.e. in behaviorally sensitized rats.

Our results agree with those of Prasad *et al.* (27) who found that ADX performed before or after treatment with COC blocked or had no effect, respectively, on the locomotor response to a challenge dose of the psychostimulant; they concluded that endogenous corticosteroids played a role in the initiation (development) but not expression of the COC-induced sensitization. However, regarding the effect of ADX on initiation of that

phenomenon, those authors demonstrated its blockade only when sensitization was examined after early withdrawal (1 day), but not at a later withdrawal time (12 days). Our study has demonstrated that ADX blocks the development of cocaine-induced sensitization, examined 5 days after cessation of the drug treatment. This observation may suggest that an effect characteristic of early withdrawal appears even after 5 days. The above conclusion is in line with the results of several studies on the mechanisms mediating behavioral sensitization to psychostimulants. Actually, it has been reported that a challenge dose of a psychostimulant (COC, amphetamine) given to behaviorally sensitized rats does not increase extracellular dopamine levels in the nucleus accumbens until day 7 of withdrawal (28, 29), but it elevates the amine concentrations in the same brain structure at later withdrawal times (30, 31). In other words, the psychostimulant (e.g. COC)-induced sensitization, manifested at both early and late withdrawal, may be mediated by different (i.e. non-dopaminergic and dopaminergic, respectively) mechanisms and in consequence, may be differently susceptible to ADX. However, it should be stressed here that initiation of the COC-induced behavioral sensitization clearly depends on dopamine release in the ventral tegmental area (6), a structure provided with glucocorticoid receptors (16). Thus — possibly via modification of gene expression (32) — endogenous corticosteroids may modulate the activation of dopamine neurones in this brain structure. Hence the removal of corticosteroids by ADX may alter the process of development of the COC-induced sensitization.

In our experiment we have also found that ADX does not affect the locomotor hyperactivity induced by a single dose of COC (day 1 of experiment 3; *Fig. 3*). This observation is somewhat surprising, since other authors reported that not only ADX, but also the corticosterone synthesis inhibitor metyrapone and corticosteroid receptor antagonists inhibit the locomotor response to acute administration of the psychostimulant (33, 34, 35). However, at least as regards the inhibitory effect of ADX, it was found when the hyperactivity was evoked by a dose of 15 mg/kg of COC or higher, but not by lower ones (33), while in our study we used a dose of 10 mg/kg of the drug.

As has already been mentioned in the Introduction, only one report has described so far the effect of CORT on the COC-induced sensitization. Thus Ortiz *et al.* (26) found that in Fisher rats which did not become behaviorally sensitized to the repeated treatment with the psychostimulant, supplementation with CORT pellets triggered development of sensitization to the drug. Our results both confirm and extend this observation, as we have demonstrated that intraperitoneal administration of CORT augments not only the development but also the expression of COC-induced sensitization. Indeed, we found that the locomotor effect of a challenge dose of COC (day 10 of experiment 1) was increased in animals treated with CORT (10, but not 5, mg/kg) plus COC (days 1–5) compared to rats receiving COC alone (*Fig. 1*). Similarly, a combination



of a challenge dose of COC and CORT, 10 mg/kg (on day 10 of experiment 2) potentiated the response of COC-sensitized rats (*Fig. 2A*). Moreover, we also observed for the first time CORT/COC or COC/CORT cross-sensitizations, since in rats treated with CORT, 10 mg/kg, alone (days 1–5) a challenge dose of COC (on day 10 of experiment 1) produced hyperactivity comparable to that induced in COC-treated (on days 1–5) animals (*Fig. 1*), and since in rats treated with COC (on days 1–5) a challenge with CORT (on day 10 of experiment 2) increased locomotor activity (*Fig. 2B*); such an effect was not observed in non-sensitized animals (on day 1 of experiment 1; *Fig. 1*). Importantly, all the above effects seem to be specific, since they are not conditioning phenomena as a challenge with SAL (on day 8 of experiment 1) does not discriminate between groups treated with SAL, COC, CORT or CORT+COC (*Fig. 1*), and since CORT does not affect the locomotor response to a single dose of COC (day 1 of experiment 1; *Fig. 1*).

It is also noteworthy that our results on the effects of ADX and CORT on the COC-induced sensitization agree with those concerning the effect evoked by another psychostimulant, amphetamine. Actually, ADX was found to abolish the development of amphetamine sensitization (25), while prolonged treatment with CORT was shown to induce cross-sensitization to the psychostimulant in rats (22), and to augment the initiation of the amphetamine-induced sensitization in mice (24).

Augmentation of the COC-induced sensitization by CORT, as well as CORT/COC cross-sensitization resemble the effects evoked by repeated stress. In fact, the exposure of rats to various stressful situations which activate the hypothalamo-pituitary-adrenal axis and lead to secretion of glucocorticoids (19) increases the locomotor response to COC or amphetamine (6, 10, 11, 12, 13). Moreover, the stress-induced cross-sensitization to psychostimulants was found to be antagonized by ADX or metyrapone (12, 13, 14); this observation suggests a relationship between behavioral sensitization and CORT secretion, either effect being evoked by stress.

The above suggestion being in line with the already discussed role of endogenous CORT in the blockade of development of the COC-induced sensitization after ADX, is also supported by some other neurochemical results. For example, both stress and CORT have been found to increase the extracellular level of dopamine in the nucleus accumbens (36, 37), while stress alone potentiates COC-induced elevation of such a concentration of the amine in this brain structure (13), another — beside the ventral tegmental area — principal neural substrate of sensitization (6, 38).

In conclusion, our results indicate that CORT facilitates the development and expression of the COC-induced sensitization, while ADX blocks the initiation, but not expression of this behavioral phenomenon. These findings may be of importance to the explanation of mechanisms of psychiatric

disturbances (psychostimulant psychosis, vulnerability to drug abuse, panic disorder), which are regarded as sensitization phenomena and may thus be relevant to therapeutic strategies of their treatment. Moreover, they may also throw more light on the mechanisms involved in psychiatric side-effects of chronic glucocorticoid treatment.

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