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Shuttle-Box Deficits Induced by Chronic Variable Stress: Reversal by Imipramine Administration

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MURUA, V. S., R. A. GOMEZ, M. E. ANDREA AND V. A. MOLINA. *Shuttle-box deficits induced by chronic variable stress: Reversal by imipramine administration.* PHARMACOL BIOCHEM BEHAV **38**(1) 125–130, 1991.—Escape performance in a shuttle-box task was evaluated in rats chronically exposed to a series of unpredictable stressors either during 14 or 7 consecutive days. Failure in escape responses was observed when animals were subjected to both regimes of variable aversive situations. The association between chronic exposure to unpredictable stressors with imipramine resulted in a significant reversal of escape deficits. Furthermore, animals submitted to repeated immobilization sessions during 7 days presented similar escape response to control rats. A possible involvement of beta-adrenergic sites on this behavioral response is discussed.

Shuttle-box Escape deficit Chronic variable stress Imipramine

A large number of clinical observations have suggested that stress could act as a predisposing and precipitating factor in the onset of affective illness, specially depression (2,8).

These suggestions have stimulated experimental studies concerning the behavioral and neurochemical consequences of stress on different animal species. In fact, most animal models of depression are based on the behavioral deficits induced by stressors and the reversal of such effects following antidepressant treatments (13, 16, 19, 23). Among these models, the learned helplessness paradigm has been widely used since it is highly sensitive to agents with antidepressant properties and seems to induce a range of symptoms that parallel those present in endogenous depression (9,37). In this model, rats exposed to an uncontrollable aversive situation, usually an inescapable shock, showed later a decreased ability to escape from future aversive situations. Some authors have proposed that a lack of control on the inescapable shock interferes with the learning of a new escape task in a subsequent test (18,19). Moreover, the uncontrollability factor is present in most of the animal models of depression (13, 18, 23). Thus, chronic variable stress, a model of depression with a high degree of validity, is based on the exposure to several uncontrollable aversive stressors (13–15).

Considering that stressor uncontrollability is a critical factor to induce escape deficit and that, besides, is present in chronic variable stress, it would be reasonable to suggest that this chronic regime of stress could have an influence on escape performance to an aversive stimulus.

In order to study this hypothesis, rats were exposed to different regimes of chronic stress and tested later on their ability to escape from the electric foot-shock. Additionally, the influence of a tricyclic antidepressant drug, imipramine, on the possible chronic variable stress effects was evaluated.

METHOD

Animals

Eighty-four male Wistar rats weighing 280–350 g were used. They were maintained at 22°C and housed in standard cage (45 × 30 × 30 cm) (6 rats per cage) on a 12-h light/dark cycle with food and water ad lib. Occasionally, animals were housed in different conditions as part of the chronic stress procedure as described below.

Chronic Stress Procedure

Animals were exposed to the following stressors: 30 min of foot shock (1 mA, 1-s duration, average 1 shock/min); 24-h food deprivation in home cage; 5-min cold swim at 4°C; 24-h

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water deprivation in home cage; 60-min shaker stress (horizontal shakes at high speed); 24-h switch cage (rats were placed in a new cage located in another room); 1-min tail pinch (one long pinch); 2-h immobilization (rats were restrained in a plastic restraining device) (5,6); 24-h isolation (rats were placed individually in 30 × 15 × 15 cm acrylic cages in the housing room with food and water ad lib). Stressors were delivered throughout the lighting cycle from 10.00 to 16.00 h with the exceptions of isolation, switch cage, or food and water deprivation which lasted 24 h. The order of stress administration and the schedules of stress delivery are presented in Table 1. The stressors applied were similar to those described by Roth and Katz (25) and Molina et al. (21).

Shuttle-Box Testing

The escape-avoidance test was carried out in a two-way shuttle-box (60 × 20 × 20 cm) with Plexiglas walls fitted with a floor consisting of stainless steel rods separated by 1.0 cm. The floor was divided into two equal size chambers by means of a wood partition (1.5 cm over the grid floor). Subjects were placed in the shuttle-box, allowed to habituate to the test environment for 3 min, subsequently they were submitted to 30 avoidance trials (intertrial intervals being 30 s). During the first 4 s of each trial, a noise signal was presented. If the response did not occur within this period, a 0.8 mA shock was applied via grid floor. If the response did not occur within a 4-s duration of shock, both shock and noise signal were terminated. The escape response required was crossing to the alternative compartment of the box. The number of escape failures, referred to as the absence of crossing response during shock delivery, was recorded. The shuttle-box training was always initiated 24 h after the last stressful event.

Jump-Flinch Test

The method used was similar to that described by Pucilowski et al. (24). The measure of pain sensitivity was carried out in a Plexiglas chamber (30 × 20 × 20 cm) fitted with a floor of stainless steel rods spaced 1.0 cm apart. Each rat was placed individually in the testing chamber and received 4 series of 10 shocks (0.5-s duration) delivered at 15-s intervals in alternating ascending and descending order. The intensity range was 0.3–1.3 mA. A jump threshold is referred to as the current intensity at which the hindlimbs of the rats left the floor. The jump threshold was determined for each series, and a mean value was calculated.

Drugs

Imipramine ClH (Laboratorio Prest; 10 mg/kg IP) was dissolved in distilled water and injected daily 60 min before each stress. The injections were made in a volume of 1 ml/kg; appropriate vehicle solutions were used for control injections.

Statistics

The data were analyzed using an one-way analysis of variance and a two-way ANOVA followed by post hoc Fisher tests with a probability of type I error set at 0.05.

EXPERIMENT 1

Exposure to uncontrollable and unpredictable stress situations leads to profound behavioral alterations. In fact, most animal models of depression are based on these behavioral changes. Among the various available models, the chronic variable stress has been postulated to have a high degree of validity (37). Thus, rats submitted to a chronic variable stress regime showed a reduced locomotion to a noise stress (13–15, 25), as well as a decreased mobility in the forced swim test (12). Considering this evidence, it seems reasonable to suggest that active behavior in response to different aversive events may be modified in chronically stressed rats. In order to analyze this hypothesis, the present experiment evaluated the escape performance to an electric foot-shock in rats submitted to a chronic variable stress regime. This escape performance was tested in a two-way shuttle-box task. The chronic stress scheme used was similar to that described by Roth and Katz (25) and Molina et al. (21). Since the original procedure contains foot-shock application which may induce escape failures by itself (18), an additional experimental group was conducted, but in this case foot-shock was replaced by restraint.

TABLE 1
TREATMENT

Days	CVS	CVS/1	CVS/7
1)	ear mark	ear mark	shaker
2)	shaker	shaker	cold swim
3)	cold swim	cold swim	tail pinch
4)	switch cage	switch cage	restraint
5)	shock	restraint	shaker
6)	water deprivation	water deprivation	cold swim
7)	tail pinch	tail pinch	tail pinch
8)	food deprivation	food deprivation	TEST
9)	shock	restraint	
10)	water deprivation	water deprivation	
11)	isolation	isolation	
12)	cold swim	cold swim	
13)	shaker	shaker	
14)	switch cage	switch cage	
15)	TEST	TEST	

Procedure

Eighteen animals were randomly divided into three groups of six rats each. In the first group (CVS), animals were submitted during 14 days to a chronic variable stress procedure (one stressor was applied each day) including foot-shock sessions (Table 1). The second group (CVS/1) contained rats also submitted to a 14-day period of variable stress sessions (one stress per day), but in this case foot-shocks were replaced by 2-h restraint sessions (Table 1). The third group was made of unstressed rats and they were used as controls. All subjects were tested in shuttle-box training 24 h after the last stress event.

RESULTS AND DISCUSSION

As noted in Fig. 1, escape response deficits were identified in animals submitted to the CVS and CVS/1 regimes. An analysis of variance of the failures escape scores showed a significant effect of group, $F(2,17) = 8.06$, $p < 0.005$. Further Fisher post hoc analysis showed that the CVS and CVS/1 group did not differ from each other, but both groups showed higher failure escape as compared to the control group ($p < 0.05$). These observations suggest that escape failures during shuttle-box training are provoked by the chronic stress applied and not only due to the influence of foot-shock session in the chronic stress procedure.

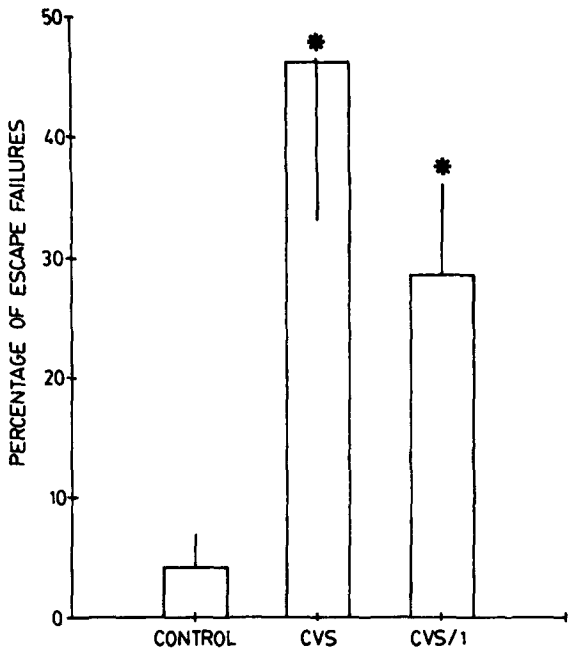

FIG. 1. Mean percentage of escape failure on 30 trials among rats treated with CVS (chronic variable stress including foot-shock session administered during a 14-day period), CVS/1 (chronic variable stress without foot-shock session during a 14-day period) and CONTROL (without stress application). n = 6 per group. *Significantly different with respect to control ($p<0.05$). Vertical lines represent SEM.

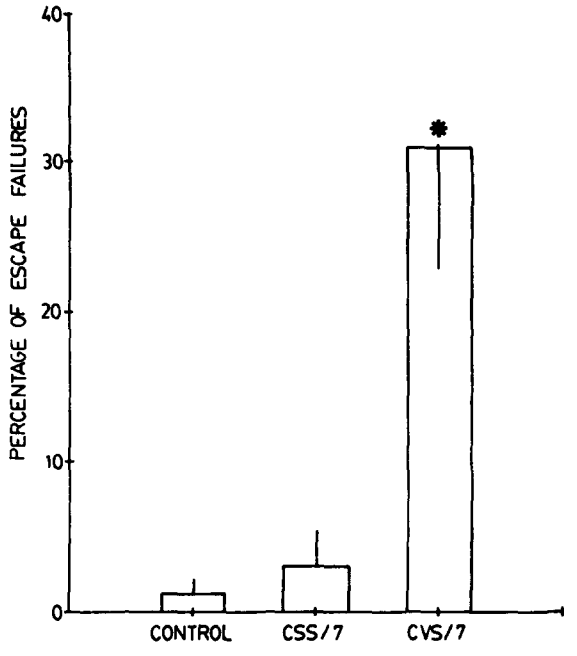

FIG. 2. Mean percentage of escape failure on 30 trials for the three groups, CVS/7 (chronic variable stress during a 7-day period), CSS/7 (chronic restraint stress during a 7-day period) and CONTROL (without stress application). n = 6 per group. *Significantly different with respect to control. Vertical lines represent SEM.

EXPERIMENT 2

Data obtained from behavioral and biochemical experiments have shown that opposite effects can be observed when different schemes of chronic stress are applied. Thus, repeated exposure to the same stressor induces different adaptive changes on monoamine sites to those described after a chronic variable stress regime (16, 21, 29, 30). These changes are involved in the behavioral responses to a variety of aversive experiences (12, 16, 20). Therefore, it seems possible that these chronic stress regimes may influence in a different way the escape performance to a foot-shock stimulus. Hence, in the present experiment, we study the effect of both stress schemes in the escape response during shuttle-box training. Rats were submitted to either seven consecutive restraint sessions (one restraint daily during 2 h) or to a regime of variable stressors over a 7-day period (one stress each day) (Table 1). The regime of at least 7 consecutive stress events was selected according to previous findings from this and other laboratories, which have reported the onset of adaptive changes on monoamine sites after the application of this scheme (5, 6, 16).

Procedure

Eighteen male rats were randomly divided into three groups of six animals each. One group was submitted to a 7-day chronic variable stress regime. Only one stressor was applied each day (CVS/7) (Table 1). Another group of rats was restrained in plastic tubes (2 h per day) over a 7-day period (CSS/7). An additional group was not submitted to stressors and served as control group. As always, shuttle-box testing was carried out 24 h after the last stress event.

RESULTS AND DISCUSSION

Rats from the CVS/7 condition exhibited a deficit in escape response (Fig. 2). On the other hand, a similar escape performance was observed between chronic restrained rats (CSS/7) and control animals (Fig. 2). An one-way analysis of variance revealed a significant effect of group, $F(2,17)=7.89$, $p<0.005$. Fisher post hoc comparisons demonstrated that CVS/7 group was different from CSS/7 group and from control group ($p<0.05$). No other difference was detected. Similar to the behavioral findings previously observed in the forced swim test (12), animals submitted to a chronic variable stress showed a higher percentage of escape failures in a shuttle-box task, as compared to those observed in rats exposed chronically to the same stressor. This evidence points out that the variability factor in the chronic stress scheme is critical in the behavioral change observed during further exposure to aversive experiences.

EXPERIMENT 3

Exposure to a regime of chronic variable stress lead to several behavioral and biochemical changes which are reversed with the concurrent administration of antidepressant drugs (13–15, 21). On the other hand, it has been previously reported that escape deficit induced by prior exposure to inescapable shock is improved by antidepressant agents (26). Considering these evidences and the results described above (Experiment 1 and 2), the aim of the present experiment was to investigate the effect of concurrent treatment with imipramine on CVS-induced escape deficit in a shuttle-box training.

Procedure

Twenty-four male rats were assigned to two experimental

groups. In the first group, animals were submitted to a chronic variable stress regime over a 7-day period (CVS/1) (Table 1). The other group consisted of control rats without stress administration. Half of the animals in each group received vehicle and the other half was administered with imipramine, in both cases injections were carried out 60 min before each stress event. Escape testing was performed 24 h after the last stress session.

RESULTS AND DISCUSSION

As previously shown (Experiment 2), a decrease in escape performance was observed in rats subjected to the CVS/7 regime (Fig. 3). Concurrent administration of variable stressors and the antidepressant drug in the same period resulted in similar escape scores as those observed in control rats (Fig. 3). Prolonged imipramine treatment in rats without stress did not modify escape performance. Two-way ANOVA revealed a significant drug effect, $F(1,23)=4.46$, $p<0.05$; a significant stress effect, $F(1,23)=9.62$, $p<0.01$; and a significant interaction between both factors, $F(1,23)=4.929$, $p<0.03$. Individual post hoc comparisons showed that the CVS/7 group was significantly different as compared to the remaining groups ($p<0.05$).

The present data suggest that in addition to the reversion of other behavioral and biochemical changes, due to CVS following imipramine administration (13–15, 21, 25), a significant reversal of escape deficits is observed in rats treated with stress and imipramine. This evidence supports the notion that this scheme of stress can be considered as an animal model of depression (37).

EXPERIMENT 4

The altered escape performance in chronically stressed rats reported in the preceding experiments may be due to changes in pain sensitivity to shock application during shuttle-box training. In order to test this possibility, chronically stressed rats with or without concurrent imipramine administration were evaluated in their pain sensitivity to foot-shock. In this study the pain threshold in the jump-flinch test was determined in rats submitted to the CVS/7 (Table 1) regime with and without concurrent administration with imipramine (10 mg/kg IP).

Procedure

Twenty-four male rats were exposed to the same stress and drug experimental protocol described in Experiment 3. Twenty-four h after the last stress situation, all animals were submitted to the jump-flinch test (described in the Method section).

RESULTS AND DISCUSSION

The application of variable stressors during 7 consecutive days with or without imipramine treatment did not change jump-flinch values. Furthermore, similar scores to control rats were obtained in animals submitted to only 7 daily injections with the antidepressant drug [mean values of current intensity (mA) that evoked the jump response, ± SEM: control-vehicle = 0.7 ± 0.1, control-imipramine = 0.7 ± 0.05, CVS/7-vehicle = 0.65 ± 0.05, CVS/7-imipramine = 0.65 ± 0.05; n = 6 per group]. The present results indicated that escape deficits after CVS/7 exposure are not induced by changes in pain sensitivity during shock application. Moreover, reversal by imipramine treatment is not mediated by modification of shock perception.

GENERAL DISCUSSION

Animals subjected to a chronic variable stress regime during 14 consecutive days failed to acquire an escape response when tested for shuttle-box responding. In the same way, difficulty in escape response was also obtained when only 7 variable stress sessions were applied. Besides, escape performance was not modified in those rats submitted to 7 immobilization sessions, suggesting that variability and unpredictability during the stress regime are critical factors in the induction of escape deficits. In accordance with this suggestion, it has been previously reported that predictable stress, unlike unpredictable stress, does not result in escape deficit or behavioral alterations (28,33). Therefore, these data might in fact support the notion that different behavioral consequences are provoked when the same or variable chronic stress paradigm are applied. In fact, other authors have described opposite effects in the forced swimming test after both chronic stress regime. Thus, repeated restraint sessions provoked an anti-immobility response (22), while the application of variable stressors similar to the chronic variable stress regime used in this study, induced a higher immobility time (12). Escape deficits were clearly reversed with concurrent imipramine administration, and the chronic variable stress regime of 7 days. Antidepressant-induced adaptation of neural systems are temporally correlated to the clinical efficacy of these drugs. Among these changes, "down-regulation" of cortical beta-adrenoceptors and subsensitivity of adenylate cyclase to noradrenaline and isoprenaline (1,32) seem to be more critically involved in antidepressant therapy. In the same way, a repeated exposure to the same stressor has been reported to induce similar changes on monoaminergic sites as those produced by antidepressant treatment (5, 6, 29–31). Thus, a reduced density of central beta-adrenergic sites was observed following persistent immobilization events (29).

We have recently described that rats submitted to a chronic variable stress regime, similar to that used in the present work,

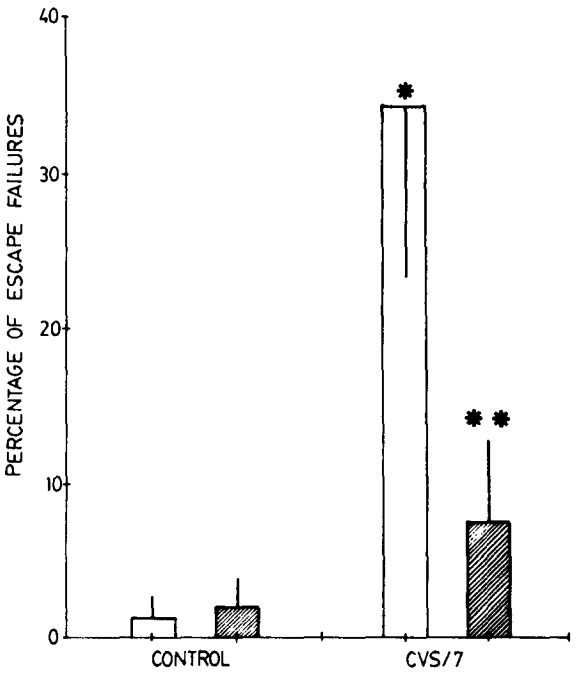

FIG. 3. Mean percentage of escape failure on 30 trials as a function of stress (CVS/7, chronic variable stress during a 7-day period; CONTROL, without stress application) and drug treatment (vehicle or imipramine). Open bars represent rats injected with vehicle and slashed bars represent rats injected with imipramine (10 mg/kg IP). *Significantly different from control, **significantly different from CVS/7 vehicle-treated rats. n = 6 per group. Vertical lines represent SEM.

have an increased number of cortical beta-adrenoceptors (21). Stimulation of beta-adrenoceptors induces an inhibition of active behaviors (11,17). Therefore, when an "up-regulation" of these adrenergic receptors is induced, behavioral inhibition may be facilitated. Consistent with these data, the present results showed a clear increase in escape deficits when chronic variable and unpredictable stress events are applied, but not after persistent exposure to the same stressor. Moreover, escape deficits are normalized to control values in stressed rats administered with imipramine. Similarly, the enhanced density of beta-adrenoceptors following the chronic variable stress regime is reduced when imipramine was concurrently injected (21). According to these observations, reversal of escape deficits in shocked rats was described after repeated administration with beta-adrenergic agonists (20).

In this line, it is important to point out that previous reports evidenced that alterations in the noradrenergic system, principally in the locus coeruleus region, are involved in stress-induced behavioral deficits (34–36). Moreover, it has been proposed that an augmented stimulation of adrenoceptors, including beta-adrenoceptors, outside the locus coeruleus region might be implicated in this behavioral alteration (35). Thus, these data support the notion that a behavioral inhibition is probably facilitated when an "up-regulation" or an enhanced stimulation of beta-adrenergic sites is produced.

Interestingly, difficulty in escape performance has been reported to occur after a single administration of FG 7142 (10), a drug that mimicked behavioral and neurochemical effects of stress stimuli (3, 4, 7). In addition, an increased number of beta-adrenoceptors in brain tissue was observed after an unique injection of this anxiogenic compound (27).

Finally, the comprehension of the central mechanism involved in the behavioral deficit induced by chronic variable stress may help to understand the alterations present in the course of affective illness.

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