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Antidepressants Reverse the Inhibition of Shock-Induced Aggression Elicited by a Prior Inescapable Shock[1]

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CUADRA, G. R. AND V. A. MOLINA. *Antidepressants reverse the inhibition of shock-induced aggression elicited by a prior inescapable shock.* PHARMACOL BIOCHEM BEHAV **40**(1) 69–73, 1991.—Animals were exposed to long-duration inescapable shock (IS) and six days later submitted in pairs to a foot-shock session in order to induce shock-elicited aggression (SIF). Shocked rats subsequently displayed a lower aggressive response as compared to unshocked animals. This reduction was prevented by repeated treatment with different antidepressant drugs administered either prior or following IS exposure. In addition, rats chronically administered with antidepressant drugs before the IS showed less inactivity during the application of the uncontrollable aversive event. These data indicate that persistent administration with these pharmacological compounds prevent the induction and impede the further expression of the reduced aggressive response induced by a previous IS.

Antidepressant Inactivity Uncontrollable shock Shock-induced fighting

EXPOSURE to previous aversive experiences leads to a series of behavioral and physiological changes (15, 21, 22, 35). Among the behavioral alterations, it was demonstrated that rats submitted to an inescapable shock (IS) showed deficits in escape performance, increased immobility in the forced swim test and reduced locomotion (15, 21, 27, 34). Most of these behavioral changes were normalized following repeated treatment with different antidepressant drugs (19, 23, 28, 32, 35).

In addition, exposure to an IS results in a decrease of aggression and social dominance (20, 26, 30). Thus it was reported that IS, unlike escapable shock, provoked a reduction in the frequency of shock-induced fighting (SIF) (20).

Taking into account that some behavioral consequences of IS exposure are reversed following antidepressant drugs, it seems conceivable that these pharmacological agents could also affect the aggressive response during foot-shock experience in rats previously submitted to an IS event. Therefore, the purpose of the present research was to investigate the influence of several antidepressant drugs, acting through different mechanisms, injected either before or after IS application, on the aggression displayed during the exposure to a foot-shock experience.

METHOD

Animals

Male adult (3-month-old) Wistar rats weighing 250–300 g were used at the start of the experiment. They were maintained on a 12-h light-dark cycle (light off at 7 p.m.) with food and water freely available.

Apparatus

Shock pretreatment ocurred in a 30 × 30 × 30-cm chamber, and SIF was conducted in a 25 × 25 × 22-cm chamber. In both, the front viewing wall was made of Plexiglas, and the remaining walls were constructed of stainless steel. The floor was fitted with a stainless steel grid from which scrambled shock was delivered.

Procedure

Subjects were individually placed in the shock pretreatment chamber and received either no shock (No-IS) or 10 trials of IS (1 mA) of 15-s duration at intervals of 30 s. Throughout, inactivity behavior was recorded during each shock trial. Inactivity was defined as the lack of all visible movement of the body with all four paws on the floor. A trial was considered inactive when the animal remained at least 10 s in an inactive posture. Thus the percentage of inactive trials for each rat was calculated.

Six days afterwards, rats from each group were randomly paired and then subjected to a session of SIF. This consisted of delivering 50 footshocks (2 mA) of 0.5-s duration at intervals of 15 s to each pair of rats, and the number of aggressive attacks was recorded. An aggressive attack was defined as a directed

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movement toward the opponent which resulted in contact, including at least one additional response of the following: biting, sparring, upright attack posturing or a supine submissive posturing, adopted by the attacked rat. This criterion has been successfully used previously by Eichelman (10) and is similar to that used by other workers (1,5).

Drug Procedure

The drugs used in the present study were: desipramine (DMI), phenelzine (PHEN) (both from Lab.Prest, Bs.Aires, Argentina), and clorimipramine (CMI) (from Ciba-Geigy, Bs.Aires, Argentina). All drugs (doses calculated as free bases) were dissolved in physiological saline in a solution of 5 mg/ml or 10 mg/ml and administered intraperitoneally (IP) at a daily dose of 5 mg/kg or 10 mg/kg over 6 consecutive days. The last injection of saline (SAL) or antidepressants in pretreated rats was carried out 24 h before the exposure to the IS. The last injection of SAL or antidepressant in posttreated rats was performed 24 h before SIF. All the injections were conducted in the morning (10–12 h) except the first SAL or antidepressants administration in posttreatment experiments, which was conducted 6 h after the IS exposure. Animals without IS were individually placed during 5 min in the shock pretreatment chamber, but no IS was applied. Hence, this study consisted of pretreatment and posttreatment experiments.

Pretreatment experiment. Rats were daily administered either with SAL or with 5 or 10 mg/kg IP of DMI, CMI or PHEN. One day after the last administration, half of the rats were exposed to the IS event. The other half were put in the shock chamber without receiving any shock. Six days afterwards, all rats (shocked or unshocked) were submitted to the SIF test.

Posttreatment experiment. Half of the animals of this treatment were exposed to the IS event, and the other half were exposed to the shock chamber without receiving any shock. After this experience, all rats were daily administered with SAL or with 5 or 10 mg/kg IP of DMI, CMI or PHEN, and one day after the last administration, submitted to the SIF test.

Statistics

The percentage of inactivity during IS and the scores of SIF were analyzed by two- or three-way ANOVA, respectively. Post hoc comparisons were done using the Newman-Keuls test. A p value of 0.05 or less was considered to represent a significant difference between treatment groups in all the experiments.

RESULTS

Figure 1 shows the effect of pretreatment with different antidepressant drugs at two doses on the percentage of inactivity during the IS. A two-way ANOVA of these data revealed a significant effect of dose, $F(1,72)=2.8$, $p<0.01$; a significant effect of drug administration, $F(3,72)=9.2$, $p<0.01$; and significant interaction between drug and dose, $F(3,72)=2.9$, $p<0.05$. As can be seen in this figure, a significant decrease in the percentage of inactive trials was observed in rats pretreated with 10 mg/kg of each of the antidepressants used. However, a lower dose (5 mg/kg) did not modify the percentage of inactive trials as compared to SAL control rats. All these individual comparisons were confirmed by Newman-Keuls post hoc test ($p<0.01$).

Figure 2 displays the effect of pretreatment with different antidepressant drugs on the number of aggressive attacks. As shown in this figure, previously shocked SAL rats had reduced SIF as compared to unshocked SAL rats. Moreover, at 10 mg/kg DMI, CMI or PHEN as well as DMI (5 mg/kg) reversed the decrease on the number of fightings elicited by a previous IS

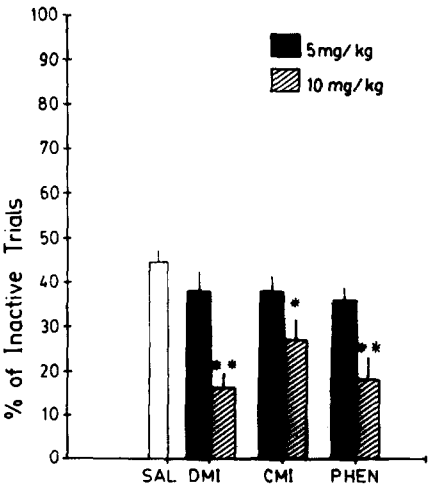

FIG. 1. The effect of SAL or different antidepressant drugs (DMI, CMI or PHEN, 5 or 10 mg/kg/day IP) on inactivity during shock exposure. Each bar represents mean percentage (±SEM) of inactive trials along 10 successive shocks. A trial was considered inactive when the animal remained at least 10 s in an inactive posture. IS = inescapable shock. Rats were daily administered with either SAL or different antidepressant drugs over six consecutive days. One day after the last administration of SAL or antidepressants, all rats were exposed to an IS session (10 shocks, 1 mA/15 s). N = 10 per group. * vs. SAL-treated rats ($p<0.05$); ** vs. SAL-treated rats ($p<0.01$).

session. CMI and PHEN did not alter SIF in previously shocked rats when they were administered a dose of 5 mg/kg. In any case, these drugs altered the scores of SIF in unshocked animals. These observations were confirmed by a Newman-Keuls post hoc test ($p<0.01$). Three-way ANOVA revealed a significant shock effect, $F(1,64)=559.5$, $p<0.01$; a significant drug effect, $F(3,64)=35.4$, $p<0.01$; a significant dose effect, $F(1,64)=167.3$, $p<0.01$; and a significant interaction between shock, drug and dose, $F(3,64)=34.2$, $p<0.01$.

As observed in Fig. 3, posttreatment with the three antidepressant drugs blocked the decrease on the aggressive behavior due to prior IS when they were injected at a dose of 10 mg/kg. Similar to the pretreatment schedule, postadministration with the three antidepressants did not alter the number of aggressive attacks in unshocked rats at any of the doses used. Moreover, only DMI-treated rats (10 mg/kg), which were previously shocked, showed an increased number of fighting episodes as compared to SAL or DMI (10 mg/kg) unshocked animals (Fig. 3). Individual comparisons were confirmed by Newman-Keuls post hoc tests ($p<0.01$). A three-way ANOVA revealed a significant shock effect, $F(1,64)=269.9$, $p<0.01$; a significant drug effect, $F(3,64)=27.11$, $p<0.01$; a significant dose effect, $F(1,64)=169.5$, $p<0.01$; and a significant interaction between shock, drug and dose, $F(3,64)=28.4$, $p<0.01$.

DISCUSSION

The present research shows that a previous exposure to an uncontrollable aversive event such as an IS leads to a clear reduction of a subsequent shock-elicited aggression. The present findings confirm previous reports that rats submitted to uncontrollable shocks were later less aggressive in an SIF situation than animals exposed to an escapable aversive experience (20). In addition to this behavioral response, exposure to an uncontrollable stressor induces behavioral impairments in a number of

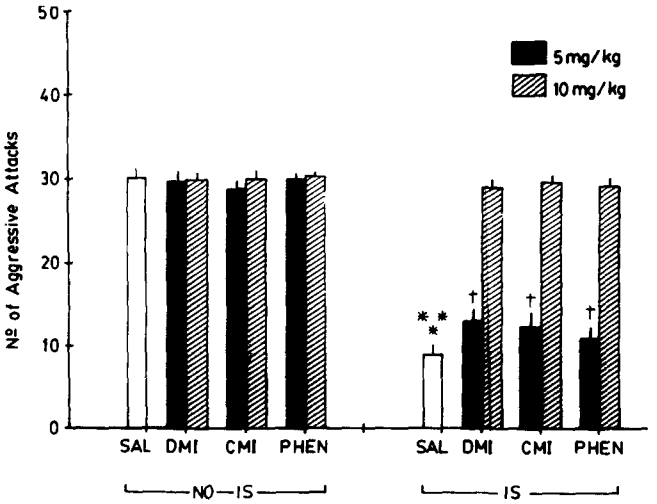

FIG. 2. Effect of the preadministration of SAL or antidepressant drugs (DMI,CMI or PHEN, 5 or 10 mg/kg/day IP) on SIF. Each bar represents the mean ± SEM of aggressive attacks. IS = exposure to inescapable shock, No-IS = no exposure to inescapable shock. Rats were daily administered with either SAL or different antidepressant drugs over 6 consecutive days. One day after the last administration, rats were either exposed to 10 trials of IS or to the shock chamber without receiving any shock. SIF was conducted 6 days after shock pretreatment. N = 5 pairs of rats per group. * vs. IS DMI (5 mg/kg) ($p<0.05$); ** vs. No-IS SAL vs. IS DMI, IS CMI and IS PHEN (10 mg/kg) ($p<0.01$) + vs. No-IS DMI, No-IS CMI and No-IS PHEN (5 mg/kg) and vs. IS DMI, IS CMI and IS PHEN (10 mg/kg) ($p<0.01$).

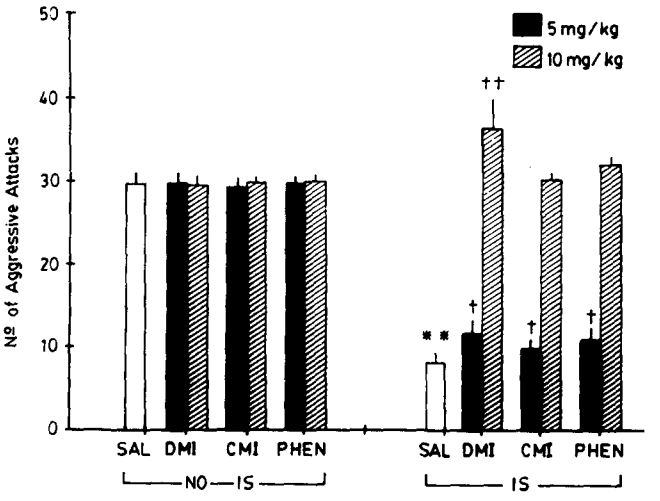

FIG. 3. Effect of the postadministration of SAL or different antidepressant drugs (DMI, CMI or PHEN, 5 or 10 mg/kg/day IP) on SIF. Each bar represents the mean ± SEM of fighting episodes. IS = exposure to inescapable shock, No-IS = no exposure to inescapable shock. Rats were daily administered with either SAL or different antidepressant drugs over 6 consecutive days after IS exposure. SIF was conducted 24 h after the last SAL or antidepressant administration. N = 5 pairs of rats per group. ** vs. No-IS SAL vs. IS DMI, IS CMI and IS PHEN (10 mg/kg) ($p<0.01$) + vs. No-IS DMI, No-IS CMI and No-IS PHEN (5 mg/kg) and vs. IS DMI, IS CMI and IS PHEN (10 mg/kg) ($p<0.01$) + + vs. No-IS DMI (10 mg/kg) ($p<0.01$).

paradigms, including shuttle escape, locomotion, forced swim, appetitive tasks and social dominance (15, 21, 27, 34, 36).

Much evidence has shown that many of these stress-induced behavioral deficits are reversed after repeated antidepressant treatments (19, 22, 23, 28, 32, 35). Our results show that, despite the difference in their mechanism of action, the three pharmacological compounds used were all effective in reversing the SIF decrease produced by the previous exposure to the IS session when they were administered at a dose of 10 mg/kg.

Previous findings have described that rats exposed to IS of long duration and moderate intensity showed changes in their activity pattern during the course of IS application (3, 12, 13). In fact, animals submitted to an IS regime similar to that used in this study showed, following a period of vigorous activity, an increasing amount of inactivity during which they accept more passively the shock (Murua and Molina, manuscript in preparation). Moreover, rats previously exposed to long-duration IS subsequently displayed a higher score of inactivity and escape deficit in a shuttle-box task, and an increased immobility in the forced swim test [(3,25), Murua and Molina, manuscript in preparation]. Chronic DMI administered before the IS reduced the inactivity displayed during IS exposure (Murua and Molina, manuscript in preparation). In support of this observation, the present work shows a clear reduction of IS-induced inactivity following the administration of the three antidepressants used at a dose of 10 mg/kg, but not after repeated treatment with 5 mg/kg. Thus these results extend and confirm previous findings concerning the reversal induced by antidepressant treatments on the behavioral inhibition provoked by a variety of different stressors (6, 16–18, 23, 29, 35). In addition, our data also indicate that antidepressant-pretreated rats had similar SIF scores to those observed in unshocked animals treated with SAL. This indicates that the decrease in inactivity during IS, like that obtained following antidepressants, might be related to the attenuation by these drugs of the reduction in SIF produced by a previous IS. Similarly, a previous report proposed that the activity displayed during a prior uncontrollable aversive event was related to the subsequent escape performance in an active avoidance task (3).

Other reports showed that acute administration of tricyclic antidepressants decreased SIF in unshocked rats (2,8). However, a subchronic treatment with a high dose of DMI (20 mg/kg) increased isolation-induced fighting in rats (33). In the same line, Eichelman and Barchas (11) reported that repeated administration with tricyclic and MAO inhibitors was all able to increase SIF. In our experimental conditions, antidepressants did not influence SIF in rats that were not submitted to an IS session. This difference could be due to different experimental treatments, since the other authors cited above determined SIF following antidepressants in rats previously submitted to SIF experiences.

The antidepressant effect was evident when a reduced aggressive response was induced by a prior stress experience. Similarly, the importance of stress-induced behavioral inhibition in revealing an antidepressant effect is also substantiated by the fact that these drugs did not alter escape performance or locomotion in nonstressed animals (16–18, 23, 28). Thereby, most of the behavioral actions elicited by these pharmacological compounds on stress-induced responses have been reported in animals showing behavioral deficits elicited by a prior stressful session (16–18, 23, 28, 35).

The most consistent and widely reported experimental finding with antidepressants is that repeated antidepressant administration leads to common adaptive changes on central monoaminergic sites (4, 24, 33). Therefore, it seems possible that these changes could be functionally related to the behavioral disinhibition observed in this study following repeated treatment with these agents.

Drugs acting at different neural systems showed preventive effects of subsequently behavioral alterations induced by shock, since they were effective in the reversal of behavioral deficits only when they were administered prior to the uncontrollable stress (9,14). Hence, these drugs act on the initial induction of behavioral inhibition but not on the further expression of behavioral deficits. From the present data, it is evident that, under our experimental scheme, prolonged antidepressant administration has preventive effects on the induction of subsequent aggressive inhibition. In addition, the fact that chronic antidepressant administration reverses behavioral inhibition in previously shocked rats suggests that these agents also affect the mechanism involved in the subsequent expression of behavioral deficits. Although additional experiments are necessary in order to elucidate the mechanism involved in the behavioral effects of antidepressant drugs under our experimental paradigm, the finding that antidepressants reverse the induction as well as the further expression of this reduced aggression may suggest that common mechanisms are underlying in both situations.

A possible effect of chronic antidepressants on pain sensitivity could contribute to the behavioral effects observed in shocked rats, which were chronically treated with these pharmacological agents. However, the fact that these drugs do not affect fighting in unshocked rats and that, according to previous reports (6, 18, 29), they also produced behavioral disinhibition in response to nonpainful stimulus may suggest that the behavioral effects of these drugs are probably not due to an alteration on nociception. In addition, some evidence has shown that the locomotion of drug-free rats chronically administered with these pharmacological compounds does not differ from vehicle-pretreated animals (7, 18, 31). Therefore, it seems unlikely that the behavioral disinhibition produced by persistent antidepressant treatment could be mediated by a generalized locomotion hyperactivity.

In conclusion, the data of this study indicate that antidepressants, acting through different mechanisms, prevent the attenuation of SIF observed in previously shocked rats. Moreover, these drugs were also effective in diminishing the further reduction of this aggressive response in rats which experienced a previous IS event.

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