Pharmacology Biochemistry & Behavior, Vol. 39, pp. 293–296. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Chronic Stress Reduces Fighting Behavior of Rats: The Effect of Antidepressants

IWONA ŻEBROWSKA-ŁUPINA, GRAŻYNA OSSOWSKA AND BOŻENA KLENK-MAJEWSKA

Department of Pharmacology, Medical School, Jaczewskiego 8, 20-090 Lublin, Poland

Received 16 October 1990

ŻEBROWSKA-ŁUPINA, I., G. OSSOWSKA AND B. KLENK-MAJEWSKA. *Chronic stress reduces fighting behavior of rats: The effect of antidepressants*. PHARMACOL BIOCHEM BEHAV **39**(2) 293–296, 1991.—The effect of chronic stress (14 various unpredictable stressors over 16 days) on electric footshock-induced fighting behavior of pairs of male Wistar rats was studied. The influence of antidepressant drugs (imipramine, desmethylimipramine, nomifensine, clomipramine, mianserine and doxepine) administered chronically (1 h before the stressor) on the aggressive behavior was also investigated in control and in stressed rats. Moreover, the effect of chronic stress on noradrenaline (NA) utilization in the brain was estimated in control and in antidepressant-treated rats. It was demonstrated that, in rats submitted to repeated unpredictable stress, the fighting behavior was significantly reduced 48 and 72 h after the last stressor. NA utilization in the brain was decreased 72 h after the stress termination. Prolonged treatment with antidepressant drugs restored the intensity of fighting behavior in stressed rats to control value as well as normalized NA utilization in the brain. It is suggested that antidepressant drugs may counteract the affective aggression deficit induced by chronic stress.

Imipramine Desmethylimipramine Nomifensine Clomipramine Mianserine Doxepine
Electric footshock-induced fighting behavior Chronic stress NA utilization

THE behavioral disturbances that follow chronic exposure to different kinds of stress in animals bear similarities to clinical depression with respect to etiology, symptomatology and responsiveness to treatment [review (2, 22, 23)]. The most significant behavioral changes observed after chronic stress are: motor activation deficit, reduced food and water consumption, decreased sleep and loss of normal aggressiveness (2, 11, 16, 21–23).

A prior history of stress is believed to be a possible precipitant of certain forms of depression in humans and may intensify a preexisting depression [review (2,22)].

In the last several years studies have demonstrated the utility of a novel animal model of depression based upon acute or chronic stress application (10, 11, 16, 21). One of the stress-dependent models of depression was developed by Katz et al. (10–12) who evoked chronic stress in rats which were subjected to a variety of unpredictable stressors over a period of 2–3 weeks.

In the present study we investigated the effect of repeated stress on electric footshock-induced fighting behavior in male Wistar rats. The influence of antidepressant drugs given chronically on the intensity of the aggressive behavior was also studied in control and in stressed rats. Moreover, the effect of chronic stress on NA utilization in the brain was estimated in control and in antidepressant-treated rats.

METHOD

Animals

Subjects in this study were male Wistar rats (180–200 g), housed six to a cage with free access to food (commercial rat chow, LSM) and water. The laboratory temperature was 18–20°C with a natural light-dark cycle. All procedures were performed between 0800 and 1400 h.

Procedure

The chronic stress regimen used was a variant of Katz et al.'s (10–12) method. Various unpredictable stressors were administered one per day (14 stressors over 16 days) as in Table 1.

Footshock-induced fighting behavior was elicited in rats after Tedeschi et al. (18,19). The pairs of male rats were placed in a glass cylinder (15 × 23 cm) on a steel grid floor for 10-min adaptation. Next, fighting was induced by electric footshock (intensity 3 mA, impulse duration 0.3 s, rate 1/s). The number of attacks (biting, boxing, fighting) were scored during 10 min of painful stimulation. At first the pairs of rats were selected for similar intensity of aggression, so that the initial mean numbers of attacks in each group were approximate. Footshock-induced fighting behavior was induced 24 h before the first session and 24, 48 and 72 h after the last session of chronic stress in the same rats. A similar procedure was used in unstressed rats.

NA utilization in the whole brain of rats was estimated as the rate of disappearance of the catecholamine after tyrosine hydroxylase inhibition with α-MT (250 mg/kg IP). The level of NA was assayed spectrofluorometrically by the method of Chang (5) as modified by Brodie et al. (4).

Drugs

The drugs used were: imipramine HCl (Polfa), desipramine HCl (Geigy), nomifensine (Hoechst AG), clomipramine HCl

TABLE 1
CHRONIC STRESS REGIMEN

Days	No.	Stressor	Time
1	1	Electric footshock (150 mA/0.2 s/2 s × 10)	20 s
2	2	Immobilization (temp. 20°C)	2 h
3	3	Electric bell	5 min
4	4	Immobilization (temp. 4°C)	2 h
5	5	Cold swim (temp. 12°C)	3 min
6	6	Light (600 W)	5 min
7–8	7	Food deprivation	48 h
9	8	Electric footshock (150 mA/0.2 s/2 s × 10)	20 s
10	9	Immobilization (temp. 20°C)	2 h
11	10	Electric bell	5 min
12	11	Immobilization (temp. 4°C)	2 h
13	12	Cold swim (temp. 12°C)	3 min
14–15	13	Food deprivation	48 h
16	14	Electric footshock (150 mA/0.2 s/2 s × 10)	20 s

(Geigy), mianserine HCl (Organon), doxepine (Polfa). All drugs, as freshly prepared solutions or suspensions, were injected IP once daily, during 14 days. Student's *t*-test was used for the statistical analysis of data.

RESULTS

The Effect of Repeated Stress on Footshock-Induced Fighting Behavior in Untreated Rats

In rats submitted to 14 various stressors the number of fighting attacks was significantly reduced (by about 60%) 48 h and 72 h after the last session of repeated stress. Twenty-four h after the stress, the intensity of fighting was diminished by about 50% (nonsignificantly) (Fig. 1).

The Effect of Chronic Treatment With Antidepressant Drugs on Footshock-Induced Fighting Behavior in Unstressed Rats

Prolonged (14 days) treatment with antidepressant drugs did not change significantly the intensity of fighting behavior in unstressed rats. Only in clomipramine-treated rats the mean number of attacks increased by about 50%, 24 and 48 h after the last dose of drug, but this effect was present only in 50% of treated animals (result not significant) (Fig. 2).

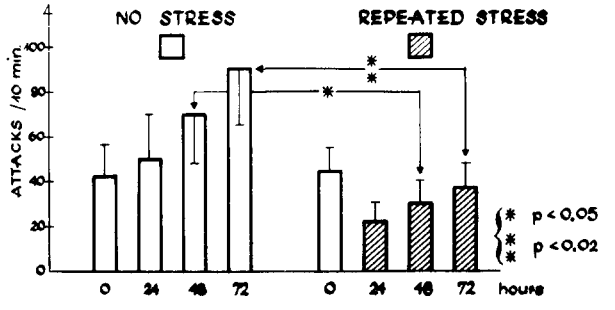

FIG. 1. The effect of repeated (16-day) stress on electric footshock-induced fighting behavior in control rats. The number of fighting attacks (mean ± SE) was recorded 24 h before the first session of stress and 24, 48 and 72 h after the last session of repeated stress in the same rats. *$p<0.05$ and **$p<0.02$ when compared to respective unstressed controls. Six pairs of rats were used per group.

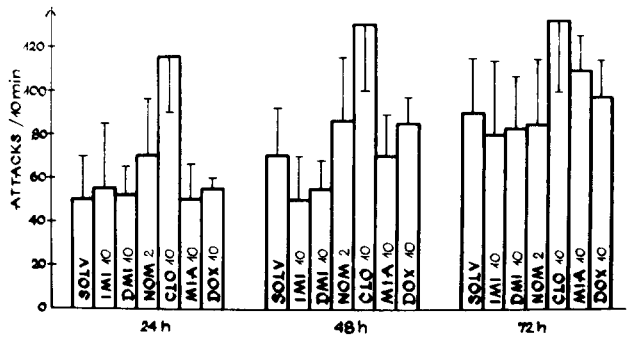

FIG. 2. The effect of chronic (14-day) treatment with antidepressant drugs on footshock-induced fighting behavior in unstressed rats. The drugs were given IP once a day in the doses: imipramine (IMI), desmethylimipramine (DMI), clomipramine (CLO), mianserine (MIA), doxepine (DOX) (all 10 mg/kg/day) and nomifensine (NOM) (2 mg/kg/day). The number of fighting attacks (mean ± SE) was recorded 24, 48 and 72 h after the last dose of drug in the same rats. Six pairs of rats were used per group.

The Effect of Prolonged Treatment With Antidepressant Drugs on Footshock-Induced Fighting Behavior in Chronically-Stressed Rats

In rats treated chronically (over 14 days) with antidepressants the number of fighting attacks increased by 150–250% 48 h or 72 h after the stress termination. These results were statistically significant (except clomipramine after 72 h) when compared with the control group (untreated-stressed rats). Twenty-four h after the last stressor only clomipramine and mianserine were effective, increasing significantly the number of attacks by about 200% (Fig. 3). The mean number of attacks in antidepressant-treated pairs of rats was similar to control unstressed-untreated rats (see Fig. 2).

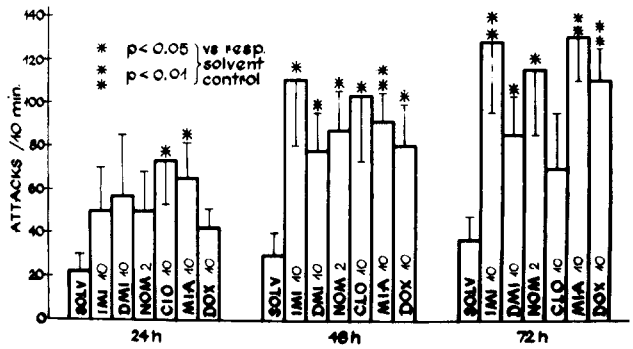

FIG. 3. The effect of chronic (14-day) treatment with antidepressant drugs on footshock-induced fighting behavior in chronically stressed rats. The drugs were given once a day 1 h before the stressor. The number of fighting attacks (mean ± SE) was recorded 24, 48 and 72 h after the last session of repeated stress in the same rats. *$p<0.05$ and **$p<0.01$ when compared to respective solvent-treated controls. Six pairs of rats were used per group. For the abbreviations and the doses of drugs see Fig. 2.

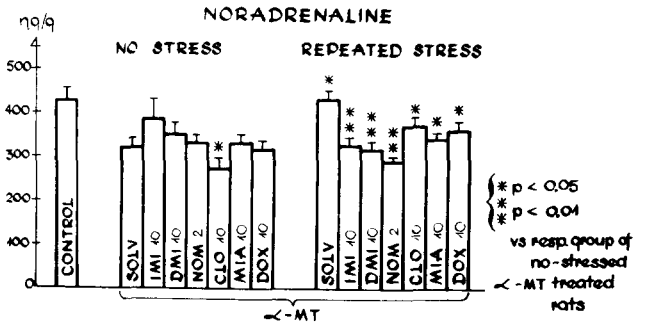

FIG. 4. Concentration of noradrenaline (mean ± SE) in whole brain (ng/g of tissue wet weight) of control and stressed rats, treated chronically with antidepressant drugs and receiving α-methyl-p-tyrosine (α-MT). Antidepressant drugs were given over 14 days, once a day, 1 h before the stressor. α-MT 250 mg/kg was administered in a single dose 72 h after the last session of repeated stress. The rats were killed 2 h after the injection of α-MT. *$p<0.05$ and **$p<0.01$ when compared to respective solvent-treated controls. Each value is the mean of 8 determinations. For the abbreviations and the doses of drugs see Fig. 2.

The Effect of Chronic Treatment With Antidepressant Drugs on NA Utilization in the Brain of Chronically Stressed Rats

Neither chronic stress nor antidepressants alone change the brain concentration of NA. In control unstressed rats α-MT decreased the level of NA by about 25%. Antidepressant drugs (except clomipramine) did not influence the effect of α-MT in these rats.

In rats submitted to chronic stress α-MT did not change the brain concentration of NA. On the contrary, in stressed rats treated chronically with antidepressants significant reduction of NA after α-MT was noted (Fig. 4).

DISCUSSION

The results of the present study demonstrate that repeated applications of various kinds of stressors (over 16 days) decreased significantly the shock-induced fighting behavior 48 or 72 h after the last session of stress. Preliminary experiments had shown that the locomotor activity measured in "open field" was not reduced 48 h after the last session of 16-day stress when compared with those of unstressed control rats (24). These results indicate that the motor functions are fully efficient after this kind of chronic stress.

Prolonged (over 14 days) treatment with antidepressant drugs restored the intensity of fighting behavior of chronically stressed rats to the normal value. This effect was also the most spectacular 48 and 72 h after the last dose of the drug.

It should be pointed out that the antidepressants used (except clomipramine) did not influence the fighting behavior in control unstressed rats. These results are consistent with those of other authors who found that shock-induced fighting was unaffected or even decreased by tricyclic antidepressants (1, 6, 9, 17). On the contrary, our results differ from those of previous papers (8,14), in which shock-induced fighting in unstressed rats was facilitated by chronic (14) or subchronic (8) treatment with antidepressant drugs. However, in those studies the facilitation of aggression was observed after other doses (20 mg/kg) of antidepressants (8) or other times of observation (2 h) after the last dose of antidepressant (14).

The main finding of our study is that repeated stress decreases the shock-induced fighting behavior and that prolonged treatment with antidepressant drugs may counteract this effect of chronic stress. These results parallel those obtained by Katz et al. (10–12) and Soblosky (16), who found that prolonged treatment with antidepressants ameliorates the other kinds of behavioral deficits due to chronic stress.

There is considerable evidence that shock-induced fighting, which is a kind of affective aggression, is primarily defensive in nature (3, 13, 15, 20). Thus it may be concluded that chronic stress decreases and antidepressant drugs given chronically activates or normalizes a defensive system in rats.

The fact that simultaneously to the recovery of the normal level of aggression the normalization of NA utilization in the brain was observed under the influence of antidepressant drugs indicates the role of NA in defensive behavior of rats. This suggestion is confirmed by the observations that piperoxane, a drug that functions as an alpha-adrenergic antagonist, facilitated shock-induced fighting at a dose of 2.5 mg/kg but inhibited the behavior at higher doses (7). On the other hand, the facilitation of shock-induced fighting by antidepressants, in chronically stressed rats, is inhibited by another alpha antagonist, prazosin, as well as by DA antagonists (24).

The participation of other neurotransmitters in the mechanism of the action of antidepressants given chronically on shock-induced fighting in chronically stressed rats is actually being studied in our laboratory.

The results of the present study suggest that: 1) Repeated stress with application of various unpredictable stressors decreases the affective aggression in rats. 2) Prolonged treatment with antidepressant drugs may counteract the affective aggression deficit induced by chronic stress.

ACKNOWLEDGEMENT

This work was supported by grant CPBP No. 06-02.I.

REFERENCES

1. Anand, M.; Gupta, G. P.; Shargava, K. P. Modification of electroshock fighting by drugs known to interact with dopaminergic and noradrenergic neurons in normal and brain lesioned rats. J. Pharm. Pharmacol. 29:437–439; 1977.
2. Anisman, H.; Zacharko, R. M. Depression: the predisposing influence of stress. Behav. Brain Sci. 5:89–137; 1982.
3. Blanchard, R. J.; Blanchard, D. C. Aggressive behaviour in the rat. Behav. Biol. 21:197–224; 1977.
4. Brodie, B. B.; Comer, M. S.; Costa, E.; Dlabač, A. The role of brain serotonin in the central action of reserpine. J. Pharmacol. Exp. Ther. 152:340–349; 1966.
5. Chang, C. C. A sensitive method for spectrophotofluorometric assay of catecholamines. Int. J. Neuropharmacol. 3:643–649; 1964.
6. Delini-Stula, A.; Vassout, A. Differential effect of psychoactive drugs on aggressive responses in rats and mice. In: Sandler, M., ed. Psychopharmacology of aggression. New York: Raven Press; 1979:41–60.
7. Eichelman B. Role of biogenic amines in aggressive behavior. In: Sandler, M., ed. Psychopharmacology of aggression. New York: Raven Press; 1979:61–93.
8. Eichelman, B.; Barthas, J. Facilitated aggression in the rat following antidepressive medication in the rat. Pharmacol. Biochem. Behav. 3:601–604; 1975.
9. Goldberg, M. E.; Horovitz, Z. P. Antidepressants and aggressive behavior. Mod. Probl. Pharmacopsychiatry 13:29–52; 1978.
10. Katz, R. J.; Hersh, S. Amitriptyline and scopolamine in animal model of depression. Neurosci. Biobehav. Rev. 5:265–271; 1981.
11. Katz, R. J.; Roth, K. A.; Carroll, S. J. Acute and chronic stress effects on open field activity in the rat: Implications for a model of depression. Neurosci. Biobehav. Rev. 5:247–251; 1981.

12. Katz, R. J.; Sibel, M. Animal model of depression: Tests of three structurally and pharmacologically novel antidepressant compounds. Pharmacol. Biochem. Behav. 16:973–977; 1982.
13. Lehman, M. N.; Adams, D. B. A statistical and motivational analysis of the social behaviours of the male laboratory rat. Behaviour 61:258–275; 1977.
14. Mogilnicka, E.; Przewłocka, B. Facilitated shock-induced aggression after chronic treatment with antidepressant drugs in the rat. Pharmacol. Biochem. Behav. 14:129–132; 1980.
15. Reis, D. J. Central neurotransmitters in aggression. Res. Publ. Assoc. Res. Nerv. Ment. Dis. 50:119–148; 1974.
16. Soblosky, J. S. Biochemical and behavioral correlates of chronic stress: Effects of tricyclic antidepressants. Pharmacol. Biochem. Behav. 24:1361–1368; 1986.
17. Sofia, R. D. Effects of centrally active drugs on four models of experimentally induced aggression in rodents. Life Sci. 8:705–716; 1969.
18. Tedeschi, D. H.; Fowler, P. J.; Miller, R. B.; Macko, E. Pharmacological analysis of foot shock-induced fighting behavior. In: Garattini, S.; Sigg, K., eds. Aggressive behaviour. Amsterdam: Excerpta Medica; 1969:245–252.
19. Tedeschi, R. E.; Tedeschi, D. H.; Mucha, A.; Cook, L.; Mattis, P. A.; Fellows, E. J. Effects of various centrally acting drugs on fighting behavior of mice. J. Pharmacol. Exp. Ther. 125:28–34; 1959.
20. Valzelli, L. Cerebral representation of aggression. In: Valzelli, L., ed. Psychobiology of aggression and violence. New York: Raven Press; 1981:75–96.
21. Weiss, J. M.; Bailey, W. H.; Pohorecky, L. A.; Korzeniowski, D.; Grillione, G. Stress-induced depression of motor activity correlates with regional changes in brain norepinephrine but not in dopamine. Neurochem. Res. 5:9–22; 1980.
22. Weiss, J. M.; Goodman, P. A.; Losito, B. G.; Corrigan, S.; Charry, J. M.; Bailey, W. H. Behavioral depression produced by an uncontrollable stressor: relationship to norepinephrine, dopamine, and serotonin levels in various regions of rat brain. Brain Rev. 3:167–205; 1981.
23. Weiss, J. M.; Goodman, P. Simson, P. Neurochemical mechanisms underlying stress-induced depression. In: Field, N.; Schneiderman, N., eds. Stress and coping. Hillsdale, NJ: Lawrence Erlbaum; 1985: 93–116.
24. Żebrowska-Łupina I.; Ossowska, G.; Klenk-Majewska, B. The influence of antidepressants on the aggressive behaviour in stressed rats: The role of dopamine. Behav. Pharmacol.; in press.