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# Facilitated Shock-Induced Aggression after Chronic Treatment with Antidepressant Drugs in the Rat

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MOGILNICKA, E. AND B. PRZEWŁOCKA. *Facilitated shock-induced aggression after chronic treatment with antidepressant drugs in the rat.* PHARMAC. BIOCHEM. BEHAV. 14(2) 129–132, 1981.—The effects of four antidepressant drugs with different mechanisms of action on shock-induced fighting between pairs of rats were determined. Amitriptyline, imipramine, mianserin and iprindole, given chronically, facilitated fighting behavior.

Shock-induced aggression Rats Amitriptyline Imipramine Mianserin Iprindole

CHRONIC administration of antidepressant drugs considerably facilitates the occurrence of aggressiveness induced by apomorphine in rats [6], and also potentiates the aggressive behavior evoked by clonidine in mice [7]. Eichelman and Barchas [4], who used another model of aggressive behavior, footshock fighting in rats, observed that repeated doses of some tricyclic antidepressants doubled attack episodes in comparison with the pretreatment level.

The present study is an extention of the findings of Eichelman and Barchas [4]. Our purpose was to test the effect of chronically administered antidepressants with different mechanisms of action on the aggressive behavior of rats in the footshock fighting model. In addition to the tricyclic drugs imipramine (IMI) and amitriptyline (AMI), which inhibit noradrenaline (NA) and 5-hydroxytryptamine (5-HT) uptake, we also examined two atypical antidepressants: mianserin (MIA), which is reported to be a potent 5-HT receptor blocker [8] as well as an effective blocker of the presynaptic $\alpha$-adrenoreceptor [1], and iprindole (IPR) a drug with a still unknown mechanism of action.

## METHOD

Male Wistar rats, 180–220 g, were housed in groups of 10 animals per cage (each cage measuring 40×31×27 cm) and had free access to food and water throughout the experiment. Twice a day they received intraperitoneal injections of drugs—AMI, IMI, MIA, IPR—or saline for 10 consecutive days, chronic experiment; or twice a day an injection of saline for 9 consecutive days and on the 10th day a single dose of the drugs tested, acute experiment. All of the drugs were administered in a dose of 10 mg/kg. Immediately after the last injection of saline or drug, the animals were placed separately in wire cages, 20×20×23 cm, for 2 hr and were then transferred to a shock box, 25×25×42 cm. After a 5 min adaptation period a partition separating a pair of rats was removed and fighting was induced by an electric footshock. Shock was delivered every 1 sec for 5 min at 2 mA intensity and 0.4 sec duration.

The latency of the first attack, the number of attacks, and the duration of fighting were assessed during the 5 min test period. An attack was scored when the experimental animal responded to a shock by assuming an upright posture and facing its partner. Time of fighting was the total time spent by rats in an upright position during the 5 min period of stimulation. In an additional test, the same chronically treated rats were examined with regard to their aggressive response to a footshock after 5- and 14-day drug withdrawals. In the time between experiments the relative groups of rats were kept in the same home-cages. Pairs of rats for every experiment were chosen at random.

Each group consisted of 10–12 pairs of rats. The results were evaluated by the Student's *t*-test.

The following substances were used: amitriptyline hydrochloride, imipramine hydrochloride (Polfa) iprindole hydrochloride (Wyeth Laboratories), mianserin hydrochloride (Organon).

## RESULTS

Single doses (10 mg/kg) of AMI, IMI, MIA and IPR did not significantly change the examined parameters. IMI produced a nonsignificant increase in the number of attacks and the time of fighting.

All of the drugs examined, chronically administered, produced different effects. Two hr after the last dose they reduced the latency of the first attack. All of the drugs significantly increased the number of attacks (by about 100%) and prolonged the time of fighting. AMI and MIA extended the time of fighting by 180 and 150%, respectively.

In the same rats (chronic experiment) tested 5 and 14 days after withdrawal, no changes in latency were observed in comparison with the saline-treated rats. The number of attacks was still increased, though to a lesser extent than after

## TABLE 1

INFLUENCE OF ACUTE OR CHRONIC TREATMENT OF AMITRYPTYLINE (AMI), IMIPRAMINE (IMI), MIANSERIN (MIA) AND IPRINDOL (IPR) ON THE FOOTSHOCK-INDUCED AGGRESSION IN THE RAT, TESTED 2 HR, 5 AND 14 DAYS AFTER ADMINISTRATION OF THE LAST DOSE

| | | Acute ← --- → | | | Chronic ← --- → | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Latency | 2 hr Number of episodes | Time of fighting | Latency | 2 hr Number of episodes | Time of fighting | Latency | 5 day Number of episodes | Time of fighting | Latency | 14 day Number of episodes | Time of fighting |
| Saline | Mean | 32.5 | 10.0 | 29.3 | 39.0 | 7.7 | 36.1 | 22.1 | 9.6 | 78.7 | 34.6 | 8.0 | 58.3 |
| | ±SEM | 6.7 | 1.8 | 7.1 | 10.7 | 1.1 | 8.0 | 9.9 | 1.7 | 9.1 | 8.2 | 1.0 | 14.2 |
| | % | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| AMI | Mean | 40.4 | 9.8 | 31.9 | 17.0 | 14.2‡ | 107.0‡ | 7.5 | 14.3* | 162.6* | 18.8‡ | 11.2 | 147.1 |
| | ± SEM | 10.3 | 1.9 | 6.8 | 3.7 | 1.7 | 19.2 | 3.0 | 1.2 | 30.9 | 3.5 | 1.3 | 20.8 |
| | % | 124 | 98 | 109 | 43 | 185 | 296 | 33 | 149 | 206 | 49 | 140 | 252 |
| IMI | Mean | 26.7 | 14.6 | 42.9 | 20.2§ | 15.8§ | 67.6* | 23.4 | 10.9 | 130.3 | 28.2 | 11.2 | 94.5 |
| | ± SEM | 6.2 | 2.7 | 9.2 | 4.4 | 1.4 | 13.3 | 6.5 | 1.5 | 23.9 | 7.0 | 1.3 | 16.8 |
| | % | 82 | 146 | 146 | 52 | 206 | 187 | 106 | 113 | 165 | 82 | 140 | 162 |
| MIA | Mean | 34.4 | 12.2 | 39.0 | 12.7* | 14.5‡ | 90.3* | 14.1 | 12.7 | 132.5 | 15.5‡ | 11.3 | 89.9 |
| | ± SEM | 7.0 | 2.6 | 9.6 | 3.8 | 2.0 | 22.1 | 4.0 | 1.7 | 26.3 | 3.6 | 2.1 | 17.9 |
| | % | 106 | 122 | 133 | 32 | 189 | 250 | 64 | 132 | 168 | 45 | 141 | 154 |
| IPR | Mean | 32.7 | 8.3 | 28.5 | 12.1† | 17.3‡ | 72.3* | 18.5 | 14.5* | 151.0† | 22.5 | 10.5 | 111.3 |
| | ± SEM | 10.3 | 2.4 | 10.7 | 2.3 | 2.5 | 14.3 | 3.9 | 1.5 | 23.1 | 7.0 | 1.2 | 19.1 |
| | % | 101 | 84 | 97 | 31 | 226 | 200 | 79 | 151 | 192 | 65 | 132 | 191 |

Significantly different from saline control: *$p<0.05$, †$p<0.02$, ‡$p<0.01$, §$p<0.02$, (Student's $t$-test).
Latency is expressed in sec and time of fighting in min.

2 hr and significantly only in the animals tested after a 5-day withdrawal of IPR (Table 1). After a 14-day withdrawal of all the drugs tested, a nonsignificant 40% increase in the number of attacks was observed. The time of fighting was still significantly prolonged in the groups of rats after 5- and 14-day withdrawals of AMI and IPR. In the IMI- or MIA-treated groups a nonsignificant 60% increase in time of fighting was observed (Table 1).

## DISCUSSION

The results indicate that chronic administration of antidepressants with different mechanisms of action, such as IMI, AMI, MIA and IPR, facilitates shock-induced fighting in rats. Eichelman and Barchas [4] have observed a similar effect after repeated doses of IMI, AMI and desipramine, using different experimental regimens and fighting test conditions. Since these drugs were administered in a regimen that increased brain NA turnover, these authors postulate a noradrenergic mechanism in the facilitation. Our findings, obtained with the model of apomorphine-induced aggressiveness in rats [6], also point to an increased function of the noradrenergic system, evoked by a chronic treatment with antidepressants. It is unlikely that the facilitation of shock-induced fighting resulted from changes in the dopamine (DA) system, since the chronically administered antidepressants did not affect apomorphine stereotypy [6]. Furthermore, Senault [13] has found that apomorphine has no effect on shock-induced aggressiveness, despite the fact that, given alone in appropriate doses, it evokes fighting. It seems unlikely that cholinergic mechanisms are responsible for the changes in shock-induced aggressiveness, since increased aggressiveness was also observed after MIA and IPR which have no cholinergic action [5, 8, 17].

It is noteworthy that in the footshock fighting test MIA and IPR act in a manner similar to IMI and AMI. MIA administered chronically increases the level of the main NA metabolite, 3-methoxy-4-hydroxy-phenylglycol (MOPEG) in the rat brain [10,15]. MIA, apart from its 5-HT receptor blocking activity [8], has been shown to be an efficient presynaptic $\alpha$-adrenoreceptor blocker [1]. A blockade of presynaptic $\alpha$-adrenoreceptors would lead to an increase in NA release and thus an increase in brain MOPEG. IPR does not affect NA turnover [12]. It is likely that IPR, as has been suggested for other antidepressants by Von Voigtlander *et al.* [19], acts indirectly. IPR, which inhibits uptake of adrenaline [19], would reduce adrenergic receptor sensitivity when given chronically. Since inhibitory adrenergic receptors are present on NA cells [2] their decreased sensitivity may cause enhancement of noradrenergic activity. It cannot be excluded that the shock-induced aggressiveness enhanced by antidepressants is a result of changes in the sensitivity of NA receptors. Observations by Crews and Smith [3] and Svensson and Usdin [14] suggest that after long-term tricyclic antidepressant administration presynaptic $\alpha$-receptors are "subsensitive" to NA and therefore no longer inhibit neurotransmitter release. This subsensitivity could be the reason for increased amounts of NA released by nerve impulses. In contrast, a prolonged blockade of NA receptors may result, as can be seen in the case of DA blockers, in supersensitivity of postsynaptic NA receptors. As used in our studies antidepressants have been reported to display NA receptor blocking properties. It was found that AMI and IMI displaced the $\alpha$-adrenergic agonist WB-4101 [9,16] and similar to IPR, have an inhibitory action on NA-stimulated cAMP formation in rat cerebral cortex [9]. MIA, at higher doses than those inhibiting the effects of 5-HT-mimetics, depressed the flexor reflex and attenuated the stimulatory effect of clonidine (a NA agonist) [8]. An $\alpha$-adrenergic activity was also described in the periphery [17]. The results of U'Prichard cited by Rosenblatt *et al.* [11] point out that chronic treatment with AMI or IMI causes an increase in WB-4101 binding in the rat brain. This may be evidence of supersensitivity of postsynaptic NA receptors. Changes in the sensitivity of NA-ergic receptors can be supported by our results obtained 5 and 14 days after withdrawal of antidepressants, a time when the drugs were not present in the brain tissue. This is especially true for rats treated with AMI and IPR and tested for prolongation of fighting time.

In conclusion, our results indicate that, in addition to tricyclic antidepressant drugs, antidepressants with a different mechanism of action can facilitate the aggressiveness, possibly via enhancement of noradrenergic activity. However, the mechanism of this phenomenon requires further studies.

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