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Effects of Chronic Administration of Antidepressant Drugs on Aggressive Behavior Induced by Clonidine in Mice

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MAJ, J., E. MOGILNICKA AND A. KORDECKA-MAGIERA. *Effects of chronic administration of antidepressant drugs on aggressive behavior induced by clonidine in mice.* PHARMAC. BIOCHEM. BEHAV. 13(2) 153–154, 1980.—The effects of antidepressant drugs on clonidine-induced aggressive behavior were determined in mice. Imipramine, mianserin and iprindole used in a single dose attenuated clonidine-induced aggression. Their chronic administration enhanced it.

Clonidine-induced aggression Mice Imipramine Mianserin Iprindole

WE HAVE previously demonstrated that chronic but not acute administration of antidepressants (imipramine, amitriptyline, desipramine, clomipramine, mianserin and iprindole) in rats enhances aggressive behavior induced by apomorphine (APO) but has no effect on APO stereotypy [4]. The enhancement of APO-induced aggressiveness was supposed to be caused by an increased response of postsynaptic noradrenaline (NA) receptors for endogenous NA which is released through the dopamine-NA interaction initiated by APO. Clonidine (CLO), a NA agonist, is able to induce aggressive behavior [6]. Hence, having considered the above assumption, it may be supposed that chronic administration of antidepressants also enhances CLO-induced aggressiveness. Since CLO does not evoke a distinct aggressive behavior in rats, our experiments had to be carried out on mice. A further reason for this study was that, as it had been demonstrated previously, chronic administration of antidepressants affected the response to CLO, i.e. caused an increase in locomotor activity, whereas in animals receiving a single dose of the antidepressant locomotor activity was unchanged or decreased [3]. Antidepressants with a different mechanism of action were used: imipramine—an amine uptake inhibitor [2], mianserin—a serotonin receptor blocker [5] and probably a presynaptic NA receptor blocker [1] iprindole—a drug with a still unknown mechanism of action.

In addition an acute experimental series was carried out in order to find out which neurotransmitters participate in the phenomenon of CLO-induced aggression.

METHOD

Male albino Swiss mice weighing 20–30 g were housed in groups and had free access to food and water throughout the experiment. Drugs or saline were injected intraperitoneally twice a day for 10 consecutive days. Two or 72 hr after the last dose of antidepressant CLO was given at a dose of 20 mg/kg IP. Immediately thereafter, groups of 4 mice each (from the same home cage) were placed together in glass cylinders [7] and were observed for 1 hr. The acute experiments were performed in a similar manner. CLO was adminsitered 2 hr after the drug studied.

The following substances were used: atropine sulfate (Sigma), clonidine hydrochloride (Boehringer, Ingelheim), imipramine hydrochloride (Polfa), iprindole hydrochloride (Wyeth Laboratories), metergoline (Farmitalia), mianserin hydrochloride (Organon), phenoxybenzamine hydrochloride (Smith, Kline and French), phentolamine methanosulfonic (Ciba), propranolol hydrochloride (Polfa).

RESULTS

The effects of treatment with antidepressants on the CLO-induced aggressiveness are shown in Table 1.

Imipramine, mianserin and iprindole used in a single dose attenuated the CLO-induced aggressiveness. Their chronic administration distinctly enhanced (by over 100%) the aggressiveness when CLO was given 2 hr after the last injection of antidepressants. Such an enhancement did not occur when CLO was given (to different animals) after 72 hr.

In the acute experiment (Table 2) phenoxybenzamine, phentolamine and propranolol inhibited the CLO-induced aggressiveness, while metergoline and atropine were without effect.

DISCUSSION

According to Ozawa *et al.* [7] the CLO-evoked aggressiveness in mice results from stimulation of postsynaptic NA receptors. Our studies with phenoxybenzamine and phentolamine add further support to this concept. Lack of effect on the part of metergoline and atropine indicates that neither the serotoninergic nor cholinergic system is involved. Hence the enhancement of CLO aggressiveness caused by chronically administered antidepressants, observed at present, may point out that such administration increases the re-

TABLE 1

THE EFFECTS OF ACUTE AND CHRONIC TREATMENT WITH ANTIDEPRESSANTS ON CLONIDINE (20 mg/kg)-INDUCED AGGRESSIVE BEHAVIOR IN MICE

Pretreatment*	Number of biting attacks within 1 hr after clonidine (mean ± SEM) 2 hr Acute	2 hr Chronic	72 hr Chronic
Saline	47.9 ± 8 (15)	52.8 ± 12 (8)	52.8 ± 12 (8)
Imipramine	16.9 ± 4 (11) $p<0.01$	120.3 ± 14 (6) $p<0.02$	48.3 ± 14 (8)
Saline	47.9 ± 8 (15)	40.8 ± 13 (8)	41.3 ± 5 (8)
Mianserin	21.0 ± 5 (8) $p<0.05$	107.0 ± 16 (7) $p<0.02$	39.4 ± 14 (8)
Iprindole	32.4 ± 6 (9)	86.0 ± 6 (7) $p<0.01$	34.1 ± 6 (8)

*Clonidine was given 2 or 72 hr after a single dose (acute experiment) or after the last dose (chronic experiment) of saline or drugs. Acute—all mice received single injections of saline or drugs (10 mg/kg IP); chronic—all mice received injections of saline or drugs (2×10 mg/kg IP) twice a day for 10 consecutive days.

Aggression is expressed as the number of biting attacks among 4 mice within 1 hr after clonidine administration. Number of trials is shown in parentheses. Statistical significance of the differences was assessed by the Student's *t*-test.

TABLE 2

THE EFFECTS OF DIFFERENT DRUGS ON CLONIDINE (20 mg/kg)-INDUCED AGGRESSIVE BEHAVIOR IN MICE

Drug treatment*	Dose mg/kg	Number of biting attacks with 1 hr after clonidine (mean ± SEM)	
Saline		36.2 ± 4.0 (5)	
Phenoxybenzamine	20	1.2 ± 1.0 (5)	$p<0.001$
Saline		35.0 ± 5.6 (14)	
Phentolamine	40	14.3 ± 2.8 (7)	$p<0.02$
Propranolol	10	11.2 ± 3.7 (6)	$p<0.02$
Saline		43.3 ± 11.0 (8)	
Metergoline	0.5	30.2 ± 4.0 (8)	
Atropine	5	46.7 ± 9.0 (8)	

*Phenoxybenzamine (IP), phentolamine (IP), propranolol (IP) were injected 2 hr, metergoline (SC) was given 3 hr, atropine (IP) 1 hr before clonidine.

For other explanations—see Table 1.

sponse of the postsynaptic NA receptor to its agonists. Such an assumption would be consistent with our previous results obtained with rats in which the effect of antidepressants on the APO-induced aggressiveness was studied. To clarify the mechanism of enhanced responsiveness of the NA receptor, further studies are needed.

The supposition presented here does not mean that other mechanisms can be excluded, e.g. the β-adrenergic system may also be involved as propranolol in acute experiments inhibits the CLO aggressiveness.

As has been demonstrated by Morpurgo [6], the CLO-induced aggressiveness is inhibited by neuroleptics. It may thus be assumed that this aggressiveness results from a dopaminomimetic activity. There have been no data, however, pointing to this kind of CLO action. Besides, antidepressants administered chronically do not enhance the APO-induced stereotypy [4]. Therefore, it would rather be assumed that the presence of dopaminergic transmission is necessary to induce CLO aggressiveness. However, this aggressiveness is due to another mechanism of CLO action, most probably a noradrenomimetic one.

Von Voigtlander *et al.* [8] reported an antagonism of chronically administered antidepressants towards the CLO-induced hypothermia in mice. However, these experiments cannot be compared with ours, since a different effect (body temperature) was studied and a considerably lower dose (0.25 mg/kg) of CLO, probably affecting the NA presynaptic receptor, was used. The latter assumption is supported by the fact that hypothermia induced by that dose was inhibited by yohimbine but not by phenoxybenzamine.

The results presented in this study are another example of the experimental regimen in which chronic administration of three antidepressants displaying different pharmacological profiles in the acute experiment seems to enhance noradrenergic transmission or stimulation. It is likely, therefore, that such a mechanism should be responsible for the therapeutic activity of antidepressants occurring after long-term treatment.

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