EXPERIMENTAL STUDY OF THE ANTIDEPRESSANT PROPERTIES OF CAPTOPRIL

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Captopril, an inhibitor of angiotensin I converting enzyme, has found wide application in clinical medicine as a hypotensive agent [1]. Preliminary clinical studies revealed the antidepressive properties of captopril [3, 4, 10]. The results of the experimental study of the antidepressive properties of captopril are fragmentary and contradictory [5, 6]. Unlike most antidepressants, for instance, captopril is without serotonin-modulating properties [6] and the study of captopril by one of the most informative tests for detection of antidepressive activity, namely forced swimming [8], has not given any precise results, for the repeated injection of captopril increased the animals' spontaneous motor activity [5].

The aim of this investigation was to compare the action of captopril with that of some classical antidepressants in a series of tests used to study this class of drugs.

EXPERIMENTAL METHOD

Male albino mice weighing 18-24 g were kept on a standard diet. The experiments were conducted between 9 a.m. and 2 p.m. in summer, in a shaded building at a temperature of 23 ± 2°C. Stereotypy was assessed in standard wire cages, every 2 min for 60 min, taking note of rearing, sniffing, biting, licking, and chewing each time [9]. Thirty animals were observed at the same time.

Spontaneous motor activity was measured in a circular open field for 3 min after placing of the animal. The number of times of crossing squares, the number of inspections of holes, and the number of standings in the center and by the wall of the field were counted. The forced swimming test was carried out by the method in [8].

The test substances were given as a single intraperitoneal injection 30 min before the experiment began, and apomorphine was injected subcutaneously immediately before the animal was placed in the wire cage. All drugs were dissolved in 0.9% NaCl, in the case of apomorphine with the addition of ascorbic acid (0.1%).

The results were subjected to statistical analysis by the Mann–Whitney I test. The captopril was generously provided by Dr. G. Ya. Shvarts (S. Ordzhonikidze All-Union Pharmaceutical Chemical Research Institute, Moscow).

EXPERIMENTAL RESULTS

As Fig. 1, 1 shows, apomorphine induced stereotyped behavior in the mice, and the effect depended clearly on dose. Captopril in a dose of 25 mg/kg significantly increased the intensity of the stereotypy induced by apomorphine in a dose of 10 mg/kg. Amitriptyline in a dose of 5 mg/kg, on the other hand, inhibited stereotypy to the level of apomorphine in a dose of 3 mg/kg.

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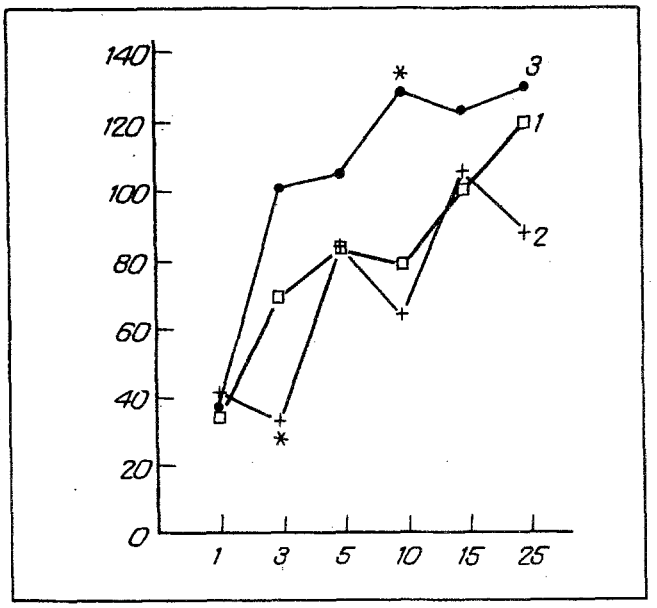

Fig. 1. Effect of captopril and amitriptyline on apomorphine stereotypy in mice. Abscissa, dose of apomorphine (in mg/kg); ordinate, intensity of stereotypy (in points). 1) Apomorphine; 2) apomorphine + amitriptyline (5 mg/kg); 3) apomorphine + captopril (25 mg/kg). Asterisk: significance of differences from effects of apomorphine at $p < 0.05$. Values given are means of not less than 6 independent experiments.

TABLE 1. Effect of Sulpiride, Haloperidol, and Amitriptyline on Apomorphine Stereotypy in Mice (M ± m)

Substance	Dose, mg/kg	No. of experiments	Intensity of stereotypy, points
Control		56	83±3
Sulpiride	10	6	66±8
	25	18	54±6*
	50	12	37±8*
Haloperidol	0,1	10	50±7*
	0,25	15	14±1*
	0,5	5	3±1*
Amitriptyline	1	5	72±9
	5	5	84±10
	20	5	117±14*

Legend. Dose of apomorphine 5 mg/kg; *) values for which $p < 0.01$ compared with control.

In the next experiments apomorphine was used in a dose of 5 mg/kg, and in this case captopril and amitriptyline, in the doses used, were ineffective.

The data in Table 1 show that, unlike the neuroleptics sulpiride and haloperidol, amitriptyline in a large dose potentiates apomorphine stereotypy. Thus, amitriptyline and captopril, in doses of 20 and 25 mg/kg respectively, potentiate apomorphine stereotypy, a characteristic feature of antidepressants which are not amonoamine oxidase inhibitors [2]. These two substances, however, differed in their effect on different manifestations of stereotyped behavior, but analysis of these data is not among the aims of the investigation. Both captopril and amitriptyline, in doses not changing the effect of apomorphine (5 mg/kg), antagonized the inhibitory action of haloperidol, whereas captopril also antagonized the action of sulpiride on apomorphine stereotypy (Fig. 2).

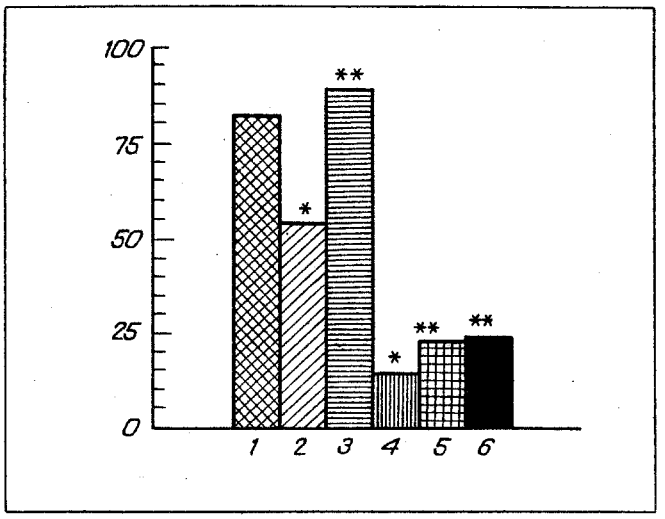

Fig. 2. Antagonism of captopril and amitriptyline relative to inhibitory effects of sulpiride and haloperidol on apomorphine stereotypy in mice: 1) control, apomorphine (5 mg/kg); 2) sulpiride (25 mg/kg); 3) sulpiride (25 mg/kg) + captopril (25 mg/kg); 4) haloperidol (0.25 mg/kg); 5) haloperidol (0.25 mg/kg) + captopril (25 mg/kg); 6) haloperidol (0.25 mg/kg) + amitriptyline (1 mg/kg). Ordinate: intensity of stereotypy (in points). Significance of differences at $p < 0.05$ level: *) compared with control; **) compared with effect of neuroleptic. Mean values of not less than 10 independent experiments are given.

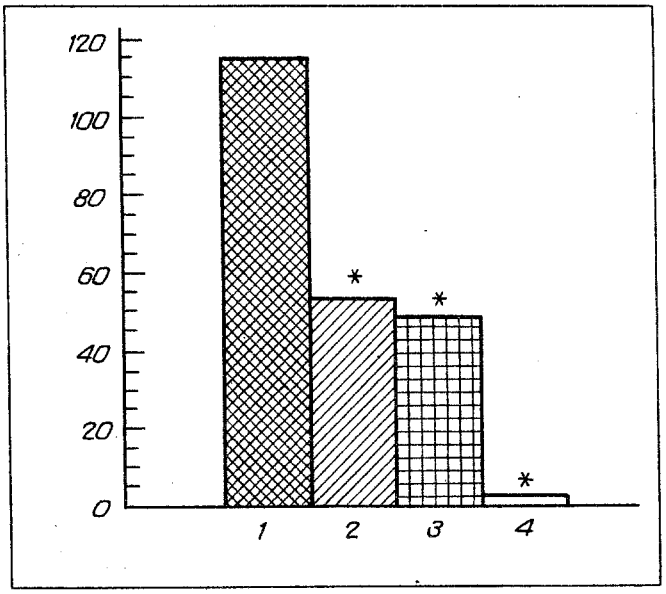

Fig. 3. Effects of captopril, imipramine, and amitriptyline in forced swimming test on mice: 1) control (physiological saline); 2) captopril (25 mg/kg); 3) imipramine (20 mg/kg); 4) amitriptyline (20 mg/kg). Ordinate: duration of immobilization (in sec). Mean values of 7 independent experiments are given. *) Significance of differences from control at $p < 0.05$.

The results indicate that captopril, like the known tricyclic antidepressants, evidently has some influence over the dopaminergic systems of the mouse brain, for it potentiates the action of agonists (apomorphine in doses affecting postsynaptic dopamine receptors) and counteracts the effect of antagonists (sulpiride, haloperidol). The total abolition of the effect of the D2-receptor antagonist sulpiride, combined with the moderate counteraction of the effect of haloperidol, which is a mixed D1- and D2-receptor antagonist, may indicate that functional interaction of captopril with the dopaminergic systems of the brain is realized at the level of type D2 dopamine receptors.

For the forced swimming test the dose and schedule of administration of captopril at which the spontaneous motor activity of the mice was unchanged was chosen: a single injection in a dose of not more than 25 mg/kg 30 min before the investigation (details not given). Under these conditions captopril, and also imipramine (20 mg/kg) and amitriptyline (20 mg/kg), likewise injected only once for the sake of comparison, shortened the duration of immobilization in the forced swimming test (Fig. 3). Under these circumstances captopril had much weaker activity than amitriptyline, and about the same as imipramine.

The results are evidence that in a series of behavioral tests used to detect antidepressive activity, there is no qualitative difference between captopril and the tricyclic antidepressants. It can be tentatively suggested that dopamine D2 receptors are implicated in the development of some of the central effects of captopril.

LITERATURE CITED

1. S. H. Croog, S. Levine, M. A. Testa, et al., New Engl. J. Med., **314**, 1657 (1986).
2. A. Delini-Stula and A. Vassout, Eur. J. Pharmacol., **58**, 443 (1979).
3. L. Germain and G. Chouinard, Biol. Psychiat., **23**, 637 (1988).
4. L. Germain and G. Chouinard, Biol. Psychiat., **25**, 489 (1989).
5. W. J. Giardina and D. M. Ebert, Biol. Psychiat., **25**, 697 (1989).
6. G. M. Goodwin and A. J. Wood, Biol. Psychiat., **22**, 1274 (1987).
7. L. Pawlowski and H. Mazela, Psychopharmacology, **88**, 240 (1986).
8. R. D. Porsolt, A. Betin, and M. Jalfre, Arch. Int. Pharmacodyn., **229**, 327 (1977).
9. M. Vasse, P. Protais, J. Costentin, and J. Schwartz, Naunyl-Schmiedeberg's Arch. Pharmacol., **329**, 108 (1985).
10. G. S. Zubenko and R. A. Nixon, Am. J. Psychiat., **141**, 110 (1984).