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Antagonistic Effect of Cyproheptadine on Neuroleptic-induced Catalepsy

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MAJ, J., E. MOGILNICKA AND B. PRZEWLOCKA. *Antagonistic effect of cyproheptadine on neuroleptic-induced catalepsy.* PHARMAC. BIOCHEM. BEHAV. 3(1) 25–27, 1975. – The influence of cyproheptadine on the neuroleptic-catalepsy in rats was studied. Cyproheptadine antagonized dose-dependently the catalepsy induced by spiroperidol, pimozide, fluphenazine and reserpine. The anticataleptic effect of two antiparkinsonian drugs, L-DOPA or amantadine was potentiated by cyproheptadine.

Cyproheptadine-Neuroleptic L-DOPA Amantadine

CYPROHEPTADINE is known to have an anticholinergic activity [1,17]. Anticholinergic substances antagonize some types of catalepsy. Moreover cyproheptadine is considered to be an antagonist of 5-hydroxytryptamine (5-HT) [5, 15, 17, 18]. According to some literature data the impaired function of the brain 5-HT-neurons (the lesion of raphe nuclei or the inhibition of 5-HT synthesis by p-chlorphenylalanine) can diminish the cataleptogenic effect of some neuroleptics [7,9]. Therefore it seemed interesting to check if cyproheptadine really influenced the catalepsy induced by neuroleptics. The effect of combined treatment with cyproheptadine plus L-DOPA or amantadine (both antiparkinsonian drugs) was also tested.

METHOD

All experiments were performed on albino Wistar rats (of both sexes) weighing 100–200 g. Catalepsy was evaluated according to Delini-Stula and Morpurgo [2], the scoring system was doubled. It means that in the case of maximal catalepsy the animal was given 6 scores at every observation. Evaluations were made at 30 min intervals for 2 hr. Thus in the case of 100% catalepsy the rat was given 24 scores jointly.

The neuroleptics were used in doses which, as it had been stated in preliminary experiments, produced catalepsy approaching that of 100%. Neuroleptics were given before the beginning of the test as follows: spiroperidol 1 hr or 2:45 hr, pimozide 3:30 hr, fluphenazine 3:15 hr, reserpine 20:30 hr. All the compounds were injected intraperitoneally; cyproheptadine, spiroperidol, pimozide, L-DOPA as suspensiom in 3% Tween 80, the remaining ones as aqueous solutions. L-DOPA was used together with a decarboxylase inhibitor Ro 4-4602, (N^1-)DL-seryl(-N^2-) 2,3,4-trihydroxybenzyl(-hydrazine), given in a dose of 25 mg/kg i.p. (in aqueous solution) 30 min before L-DOPA.

The statistical calculations were performed with the Student's *t*-test. Groups treated with spiroperidol alone, as well as groups treated with spiroperidol and cyproheptadine, consisted of 10 rats, the others of 8 rats.

The following substances were used: amantadine hydrochloride (Merz, Frankfurt), cyproheptadine hydrochloride (Merck, Sharp, Dohme Zürich), L-DOPA (Reanal), fluphenazine dihydrochloride (Polfa), pimozide (Janssen Pharmaceutica), reserpine (Rausedyl, Gedeon Richter), Ro 4-4602 (N-) D,L-seryl (-N′-)2,3,4-trihydroxybenzyl(-hydrazine) (Hoffmann-La Roche Co., A. G. Basel), spiroperidol (Janssen Pharmaceutica).

RESULTS

Effect of Cyproheptadine

After spiroperidol given alone the catalepsy score was 23.6 ± 0.2. Cyproheptadine injected 30 min after spiroperidol (0.4 mg/kg) weakened or abolished dose-dependently the catalepsy, Fig. 1. The catalepsy produced by pimozide 4 mg/kg (the catalepsy value 21.4 ± 0.6) fluphenazine 0.45 mg/kg (the catalepsy value 21.7 ± 0.6) or reserpine 5 mg/kg (the catalpesy value 24.0 ± 0), Fig. 1 was also antagonized. Cyproheptadine counteracted the spiroperidol-induced catalepsy also when it was injected 1 hr before spiroperidol.

Effect of Cyproheptadine plus L-DOPA

Cyproheptadine 0.6 mg/kg or L-DOPA 100–200 mg/kg (given together with Ro 4-4602) did not influence the catalepsy induced by spiroperidol, Fig. 2. The catalepsy was antagonized by combined treatment with cyproheptadine plus L-DOPA.

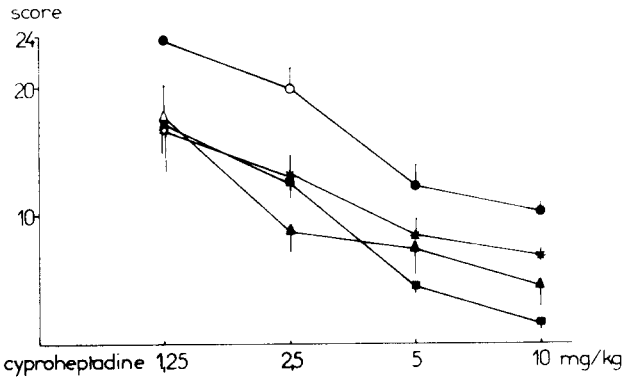

FIG. 1. The effect of cyproheptadine on the catalepsy induced by spiroperidol (0.4 mg/kg), pimozide (4 mg/kg), fluphenazine (0.45 mg/kg) or reserpine (5 mg/kg). The drugs were given before the beginning of the test as follows: reserpine 20:30 hr, pimozide 3:30 hr, fluphenazine 3:15 hr, spiroperidol 1:00 hr, cyproheptadine 0:30 hr. The catalepsy evaluations were made at 30 min intervals for 2 hr. Each result is presented as a mean of the sums of four evaluations. The statistical calculations were performed with the Student's *t*-test. The solid figures mean the results are statistically significant ($p<0.01$) ✡——✡ spiroperidol, △——△ pimozide, ○——○ fluphenazine, □——□ reserpine. The catalepsy score for the neuroleptic dose were: spiroperidol 23.6 ± 0.16; pimozide 21.4 ± 0.6; fluphenazine 21.7 ± 0.6; reserpine 24.0 ± 0.0.

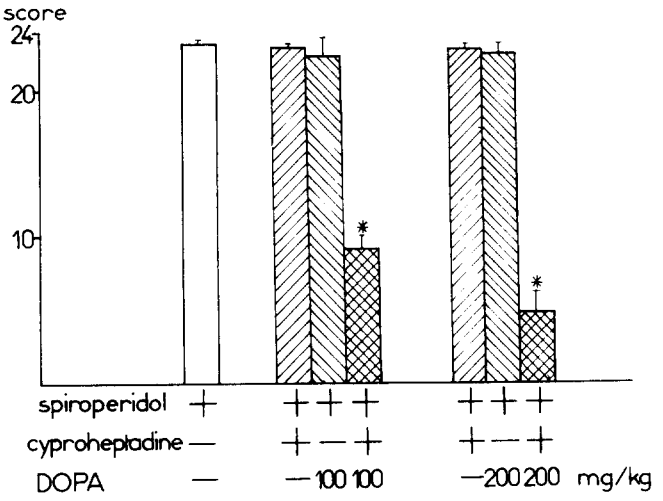

FIG. 2. The effect of cyproheptadine (0.6 mg/kg) plus L-DOPA (100 or 200 mg/kg) on the catalepsy induced by spiroperidol (0.4 mg/kg). The drugs were given before the beginning of the test as follows: spiroperidol 2:00 hr, cyproheptadine 0:30 hr, L-DOPA 0:30 hr (together with Ro4-4602 injected 30 min before L-DOPA). The catalepsy evaluations were made at 30 min intervals for 2 hr. The results are presented as means of the sums of four evaluations. The statistical significance was performed with the Student's *t*-test and indicated by asterisk.

Effect of Cyproheptadine plus Amantadine

Amantadine 10 mg/kg or 20 mg/kg diminished the spiroperidol catalepsy. Cyproheptadine 0.6 mg/kg did not influence it, Fig. 3. The combined treatment with cyproheptadine plus amantadine 10 or 20 mg/kg induced the stronger anticataleptic effect as amantadine given alone.

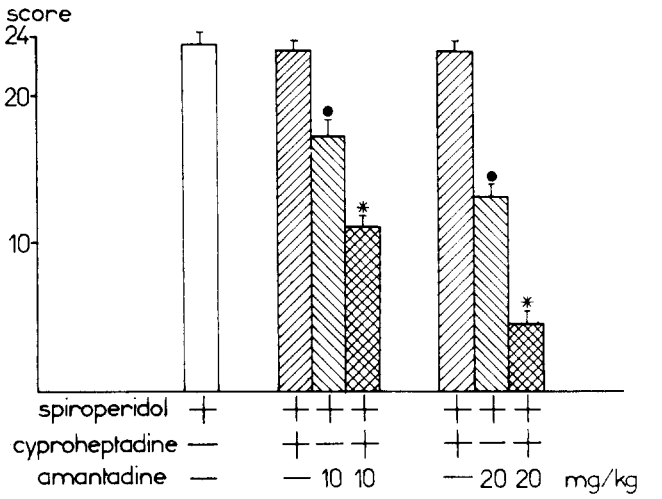

FIG. 3. The effect of cyproheptadine (0.6 mg/kg) plus amantadine (10 or 20 mg/kg) on the catalepsy induced by spiroperidol (0.4 mg/kg). The drugs were given before the beginning of the test as follows: spiroperidol 3:00 hr, cyproheptadine 1:00 hr, amantadine 0:30 hr. The catalepsy evaluations were made at 30 min intervals for 2 hr. The results are presented as means of the sums of four evaluations. The statistical significance was performed with the Student's *t*-test. ^{x}versus spiroperidol + amantadine group $p<0.02$. ^{o}versus spiroperidol group $p<0.01$.

DISCUSSION

As had been expected cyproheptadine antagonizes, according to the dose, the catalepsy induced by neuroleptics blocking dopaminergic receptors (spiroperidol, pimozide, fluphenazine) as well as those releasing catecholamines (reserpine). Cyproheptadine also potentiates the anticataleptic activity of L-DOPA. In spiroperidol-induced catalepsy after the combined treatment with cyproheptadine and L-DOPA (together with the inhibitor of peripheral decarboxylase) a marked antagonistic activity has been observed. Treatment with cyproheptadine alone or with L-DOPA in the same doses did not influence the catalepsy. Our previous experiments demonstrated that L-DOPA given in higher doses antagonized the catalepsy induced in rats by butyrophenone or phenothiazine neuroleptic, among others by spiroperidol [11,13]. The anticataleptic activity of amantadine, another antiparkinsonian drug acting by dopaminergic mechanism [3, 12, 16] was increased by cyproheptadine.

The results presented here indicate that cyproheptadine may be of importnace as an antiparkinsonian drug given separately or combined with L-DOPA. In the latter case it would make possible decreasing the L-DOPA dose and to lessen the side-effects induced by this amino acid. Cyproheptadine may also efficacious as a drug reducing the extrapramidal disturbances observed during the neuroleptic therapy.

The question arises what is the mechanism of anticataleptic effect of cyproheptadine. Probably it may be an anticholinergic atropine-like action. On the other hand atropine does not influence the reserpine catalepsy [4,19] which is antagonized by cyproheptadine. The antiserotoninergic activity presents another possibility. As has been mentioned lesions of raphe nuclei or treatment with p-chlorphenylalanine, an inhibitor of 5-hydroxytryptamine synthesis, weakens the cataleptic action of haloperidol and chlorpromazine [7,9]. The presence of numerous serotoninergic endings has been found in substantia nigra [14], so 5-HT may have an influence on the nigrostriatal system which is influenced by neuroleptics inducing catalepsy. Lesions of the substantia nigra decrease the 5-HT level in striatum and produce the extrapyramidal sings [6,8]. The antihistaminic mechanism should also not be forgotten. Cyproheptadine has such an activity [15] and the antihistaminic drugs may abolish the catalepsy [10]. The dopaminergic mechanism however, like that of L-DOPA or amantadine for instance, does not seem to be involved. Cyproheptadine given alone does not evoke excitement symptoms or stereotypy induced by drugs of this kind.

Further experiments are needed to explain the mechanism of cyproheptadine anticataleptic activity presented in this report.

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