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On the Anticataleptic Action of Cyproheptadine

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MAJ, J., J. SARNEK, V. KLIMEK AND A. RAWLÓW. *On the anticataleptic action of cyproheptadine.* PHARMAC. BIOCHEM. BEHAV. 5(2) 201–205, 1976. – The anticataleptic action of cyproheptadine, a tricyclic compound known as antiserotonin, anticholinergic and antihistaminic drug in comparison to that of atropine, promethazine, imipramine, desipramine, chlorimipramine and nomifensine was studied in rats. The catalepsy induced by spiperon, pimozide or fluphenazine was antagonized by cyproheptadine, atropine and promethazine. Imipramine and nomifensine were less active, desipramine and chlorimipramine without effect. The reserpine- and α-methyltyrosine-catalepsy was counteracted by cyproheptadine, promethazine and nomifensine, but not by atropine or tricyclic antidepressants. Only cyproheptadine and promethazine antagonized the catalepsy caused by a combined treatment with reserpine and α-methyltyrosine. The pilocarpine-catalepsy was abolished by atropine, promethazine and nomifensine and unaffected by tricyclic antidepressants. Atropine and promethazine antagonized also the physostigmine-catalepsy. The catalepsy induced by both cholinomimetic drugs was not changed or increased by cyproheptadine. The results presented indicate that cyproheptadine differs in its anticataleptic activity from all the drugs used for comparison. Possible mechanisms of this activity are discussed.

Cyproheptadine Atropine Promethazine Antidepressants Anticataleptic action

IN OUR previous paper we have shown that cyproheptadine antagonizes the catalepsy induced by spiperon, pimozide, fluphenazine and reserpine, as well as potentiates the anticataleptic effects of antiparkinsonian drugs - L-DOPA and amantadine [14]. The mechanism of this anticataleptic activity of cyproheptadine was not clear. Cyproheptadine is thought to be a serotonin receptor blocker [1, 20, 21, 22] and according to some literature data [7,12] the impaired function of serotonin neurons can counteract the cataleptogenic effect of some neuroleptics. In addition cyproheptadine possesses cholinolytic and antihistaminic properties [20,21]. It is well known that cholinolytic and antihistaminic drugs are able to antagonize some types of catalepsy. Therefore, in the present experiments we have compared the anticataleptic action of cyproheptadine with that of atropine and promethazine, using different models of drugs-induced catalepsy. Cyproheptadine is a tricyclic compound and antagonizes the catalepsy induced by reserpine. That is why we have included in our studies the following tricyclic antidepressants: imipramine, inhibiting the uptake of noradrenaline and serotonin, desipramine, affecting mainly noradrenaline neurons, chlorimipramine, which inhibits serotonin uptake. Another new nontricyclic antidepressant, nomifensine, which acts on the dopamine neurons was also tested. The part of the results of this paper was presented at the IUPHAR Congress [16].

METHOD

All experiments were performed on Albino Wistar rats (of both sexes) weighing 120–190 g. Catalepsy was evaluated according to Delini-Stula's and Morpurgo's method [3], the original scoring system being doubled. It means, that in the case of a maximal catalepsy an 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 a rat was given 24 scores jointly. Each experimental or control group consisted at least of 8 rats. Neuroleptics and α-methyltyrosine, used in doses found in our previous experiments as ED_{50}, were given before the antagonistic drugs as follows: spiperon 1 hr, pimozide 4 hr, fluphenazine 4 hr, reserpine 18 hr, α-methyltyrosine 16 hr. The catalepsy was evaluated 30, 60, 90 and 120 min after the antagonist. Pilocarpine and physostigmine were injected 1 hr following the antagonist and the catalepsy was evaluated 30, 60, 90 and 120 min later. All the drugs were injected intraperitoneally or subcutaneously (reserpine, pilocarpine, physostigmine) as aqueous suspensions in 0.5% Tween 80 (spiperon, pimozide, α-methyltyrosine, cyproheptadine, nomifensine) or dissolved in saline. The statistical calculations were performed with Student's *t*-test. Each experimental or control group consisted at least of 8 rats.

The following substances were used: atropine (Fluka); chlorimipramine hydrochloride (Polfa); cyproheptadine hydrochloride (Merck, Sharp and Dohme); desipramine hydrochloride (Ciba-Geigy); fluphenazine dihydrochloride (Polfa); imipramine hydrochloride (Polfa); α-methyltyrosine methylester (Sigma); nomifensine (Hoechst); physostigmine salicylate (Hoffmann-La Roche); pilocarpine hydrochloride (Merck, Sharp and Dohme); pimozide (Janssen Pharmaceutica); promethazine (Pipolfen, amp. Egyt); reserpine (Rausedyl amp., Gedeon Richter); and, spiperon (Janssen Pharmaceutica).

RESULTS

Spiperon-Catalepsy

Spiperon-induced catalepsy (0.4 mg/kg) was antagonized by cyproheptadine, 1.25 - 10 mg/kg (Fig. 1). Similar antagonistic effects were exerted by atropine (2.5 10 mg/kg) and promethazine (10 40 mg/kg). Imipramine reduced spiperon-induced catalepsy by about 50%, but given only in the dose of 10 mg/kg. Similar antagonistic effects were observed following nomifensine at all doses used 10, 20 and 40 mg/kg. Desipramine and chlorimipramine were without effect.

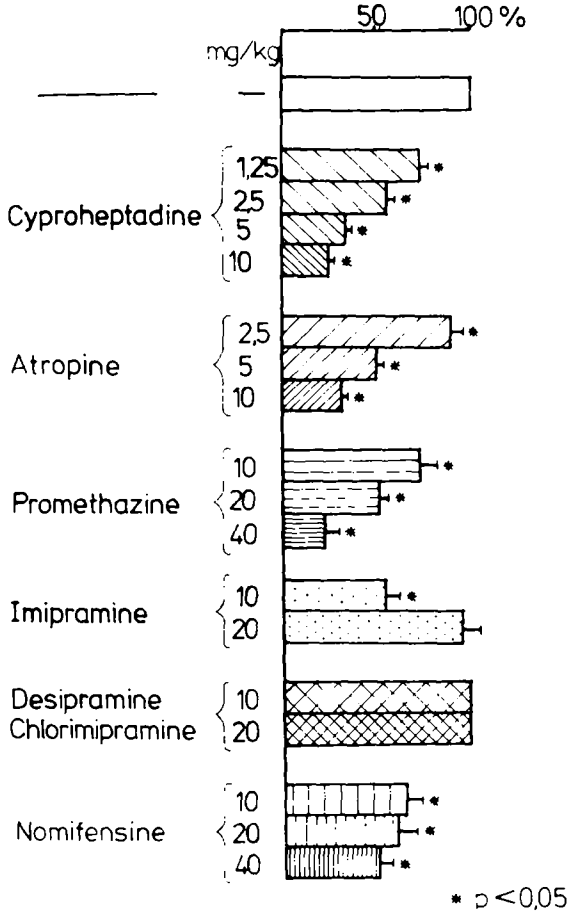

FIG. 1. The catalepsy induced by spiperon (0.4 mg/kg IP). All the drugs were given IP 1 hr after spiperon. The catalepsy was scored at 30 min interval for 2 hr (starting 30 min after the antagonist). The results are presented as percentages in relation to a group treated only by a cataleptogenic drug. The statistical significance was performed by Student's *t*-test. Spiperon, cyproheptadine, nomifensine were injected as aqueous suspensions in 0.5% Tween 80, the remaining drugs were dissolved in saline.

Pimozide- and Fluphenazine-Catalepsy

Similar results were obtained in the case of catalepsy induced by pimozide (4 mg/kg; Fig. 2) or fluphenazine (0.4 mg/kg; Fig. 3). Cyproheptadine (1.25 - 10 mg/kg); atropine (2.5 - 10 mg/kg) and promethazine (10 49 mg/kg) reversed the catalepsy in similar doses as the spiperon-catalepsy. Imipramine (10 20 mg/kg) and nomifensine (10 40 mg/kg) showed a moderate or slight antagonism, whereas desipramine and chlorimipramine were devoid of an anticataleptic activity.

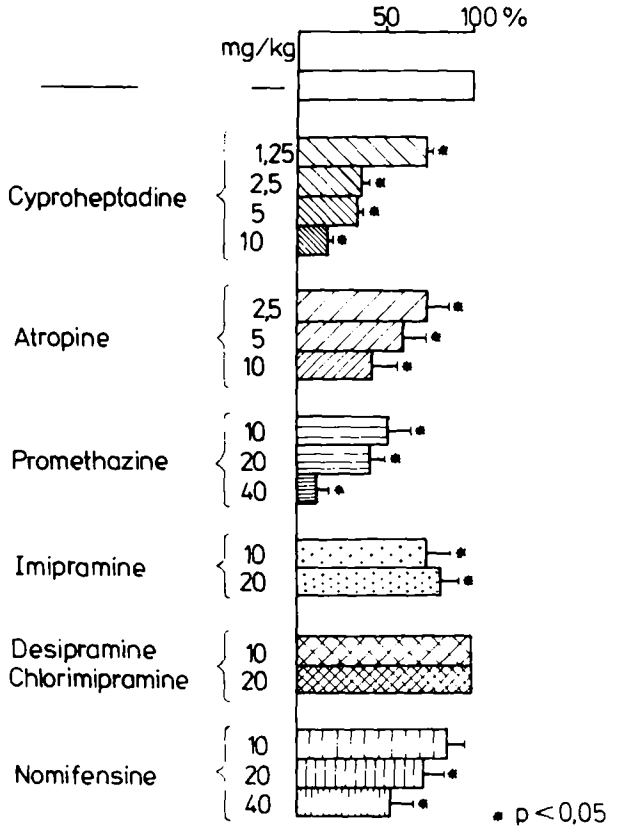

FIG. 2. The catalepsy induced by pimozide (4 mg/kg IP). All the drugs were given IP 4 hr after pimozide, which was injected as an aqueous suspension in 0.5% Tween 80. For other explanations see Fig. 1.

Reserpine-Catalepsy

The catalepsy caused by reserpine, 5 mg/kg was abolished by cyproheptadine (1.25–10 mg/kg; Fig. 4). An antagonistic effect of promethazine (10 40 mg/kg) was weaker than that towards the spiperon-catalepsy. Atropine was completely devoid of an anticataleptic activity. Nomifensine (5 40 mg/kg) reversed the reserpine-catalepsy at doses lower than those needed to antagonize the spiperon-, pimozide- or fluphenazine-catalepsy. Imipramine, desipramine and chlorimipramine were without effect.

α-Methyltyrosine-Catalepsy

The catalepsy induced by α-methyltyrosine (250 mg/kg) was antagonized by cyproheptadine (5 10 mg/kg) to a smaller degree (than other types of catalepsy), Fig. 5. Promethazine (10 - 40 mg/kg) was also less potent – its distinct anticataleptic effect was observed at a dose of 40 mg/kg. Imipramine, only in a dose of 10 mg/kg, slightly reduced the cataleptic effect of α-methyltyrosine. Nomifensine antagonized the catalepsy in dose-related manner; at the highest dose used, 40 mg/kg, the 90%-antagonism was found. Atropine, desipramine and chlorimipramine were not active.

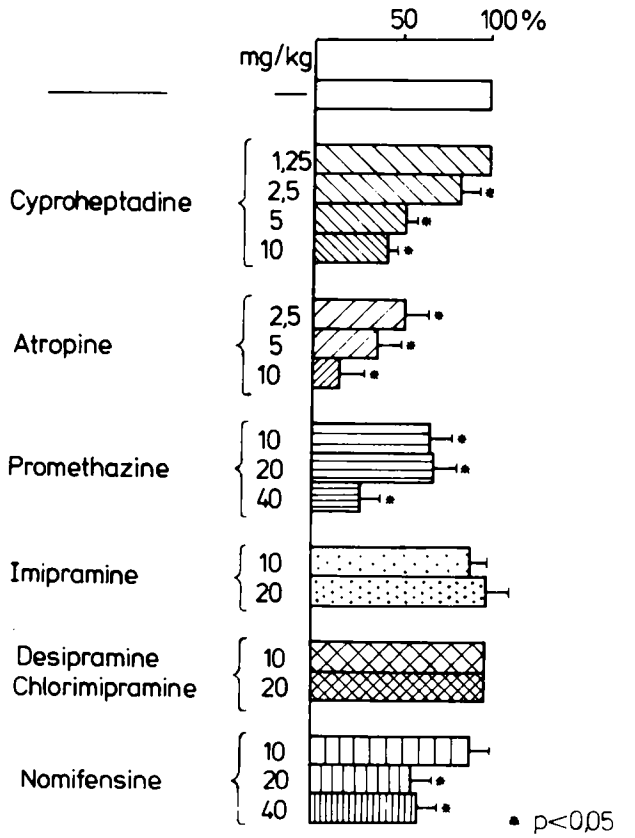

FIG. 3. The catalepsy induced by fluphenazine (0.4 mg/kg IP). All drugs were given IP 4 hr after fluphenazine, which was dissolved in saline. For other explanations see Fig. 1.

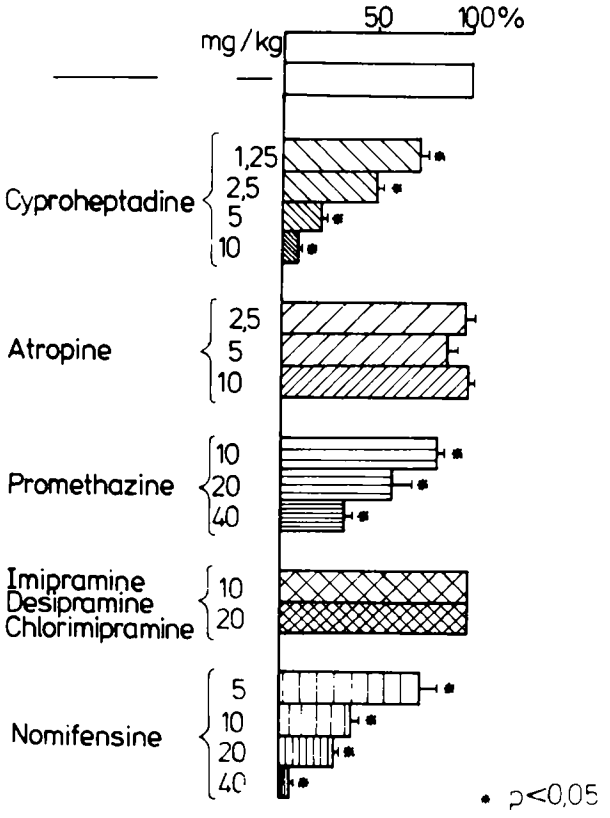

FIG. 4. The catalepsy induced by reserpine (5 mg/kg SC). All the drugs were given IP 18 hr after reserpine (from ampullae). For other explanations see Fig. 1.

Reserpine Plus α-Methyltyrosine-Catalepsy

The catalepsy elicited by a combined treatment with both reserpine (5 mg/kg) and α-methyltyrosine (125 mg/kg) was antagonized by cyproheptadine (2.5–10 mg/kg) and promethazine (10–40 mg/kg) similarly as the catalepsy produced by α-methyltyrosine alone (Fig. 6). A slight antagonism was observed following atropine (5–10 mg/kg). The anticataleptic effect of nomifensine (10–40 mg/kg) was completely abolished. Tricyclic antidepressants were without effect.

Cholinomimetics-Catalepsy

In pilocarpine-catalepsy (4 mg/kg) atropine given in doses 1.25, 2.5 and 5 mg/kg demonstrated a strong antagonism (Fig. 7). Its ED_{50} was below 1.25 mg/kg. Promethazine (10–40 mg/kg) also produced the anticataleptic effect and its active doses were similar to those which reversed spiperon-induced catalepsy. Cyproheptadine (1.25–5 mg/kg) did not counteract the pilocarpine-induced catalepsy, on the contrary, some potentiating effect could be observed. Nomifensine completely antagonized this type of catalepsy already in doses of 10–20 mg/kg, whereas imipramine, desipramine, and chlorimipramine left it unaffected.

Similar results were seen using catelepsy induced by physostigmine (3 mg/kg). Atropine and promethazine, at doses similar to those which were active towards the pilocarpine-catalepsy, antagonized the physostigmine-catalepsy. Their ED_{50} were about 1 mg/kg and 20 mg/kg respectively. Cyproheptadine, within the dose range from 0.5 to 10 mg/kg, was devoid of anticataleptic activity; in fact it showed a tendency to potentiate the catalepsy.

DISCUSSION

The present experiments support our previous results [14] and indicate that cyproheptadine possesses strong anticataleptic properties in different types of catalepsy. It antagonizes the catalepsy induced by dopamine receptor blockade (spiperon, pimozide, fluphenazine), by release of catecholamines (reserpine) or by inhibition of catecholamines synthesis (α-methyltyrosine). The exception is the catalepsy induced by cholinomimetic (at least that induced by pilocarpine and physostigmine) not affected or even increased by cyproheptadine. The comparison of cyproheptadine with cholinolytic (atropine) and antihistaminic (promethazine) indicates that all three drugs possess similar anticataleptic properties when catalepsy is induced by the dopamine receptor blockers. Distinct differences exist in the case of the catalepsy induced by reserpine or α-methyltyrosine. In these conditions cyproheptadine and promethazine demonstrate similar antagonism, whereas atropine is without effect. The lack of an antagonistic effect of cholinolytics towards the catalepsy induced by reserpine [5,23] or by α-methyltyrosine [18] was described earlier. Significant difference between cyproheptadine and atropine

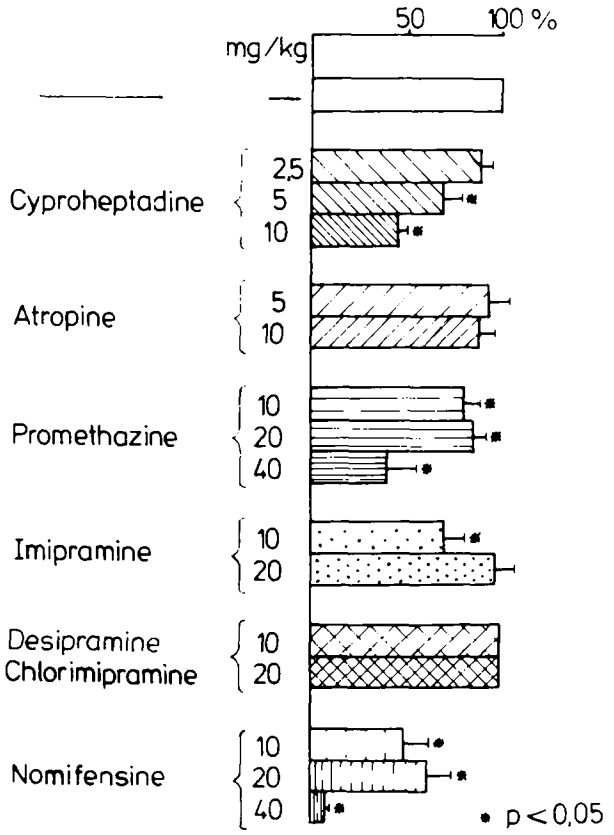

FIG. 5. The catalepsy induced by α-methyltyrosine (250 mg/kg IP). All the drugs were given IP 16 hr after α-methyltyrosine, which was injected as an aqueous solution in 0.5% Tween 80. For other explanations see Fig. 1.

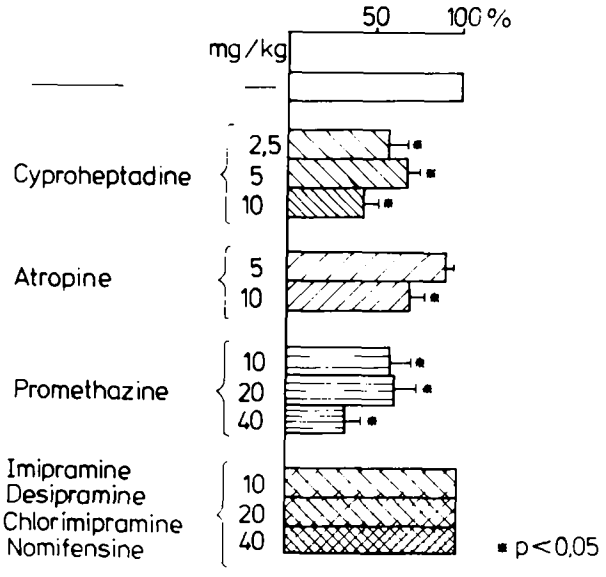

FIG. 6. The catalepsy induced by reserpine (5 mg/kg SC) plus α-methyltyrosine (125 mg/kg IP). Reserpine and α-methyltyrosine were given 18 and 16 hrs respectively before other drugs used. For other explanations see Figs. 1, 4, 5.

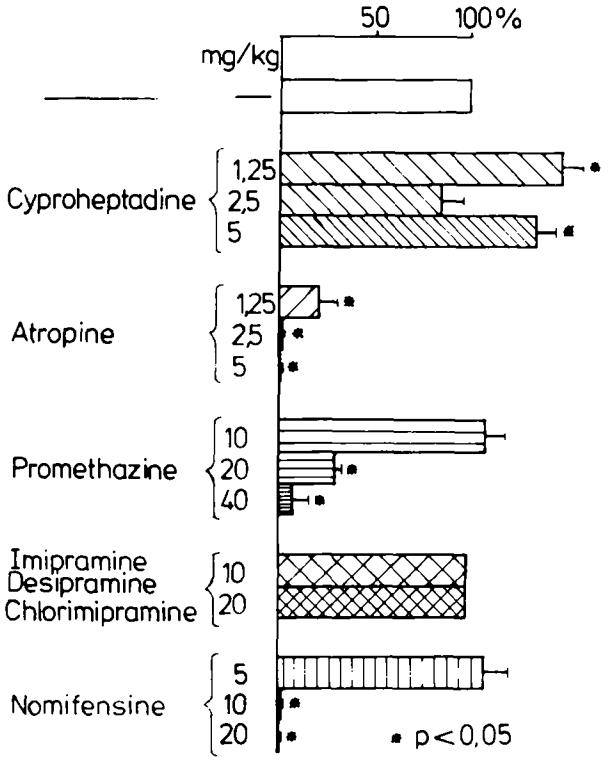

FIG. 7. The catalepsy induced by pilocarpine (4 mg/kg SC). All the drugs were given 1 hr before pilocarpine. The catalepsy was scored at 30 min intervals for 2 hr (starting 30 min after pilocarpine). Pilocarpine was dissolved in saline. For other explanations see Fig. 1.

or promethazine is present when catalepsy is induced by pilocarpine or physostigmine. Cyproheptadine does not antagonize this type of catalepsy but even potentiates it, whereas atropine or promethazine are potent antagonists. The active doses of promethazine are similar to those antagonistic in the neuroleptic-catalepsy. Atropine is more active towards the catalepsy induced by cholinomimetics. It seems therefore that the anticataleptic (antineuroleptic) effect of cyproheptadine is not a consequence of its cholinolytic activity. Cyproheptadine differs also from antidepressant drugs studied. It can be compared only with nomifensine as other antidepressants tested are not active or reveal only a slight antagonism. However, a significant difference exists even between nomifensine and cyproheptadine in their anticataleptic activity. The former, in contrast to the latter, is not active when catecholamine have been depleted by a combined treatment with reserpine plus α-methyltyrosine. In pilocarpine-induced catalepsy nomifensine, but not cyproheptadine, possesses an antagonistic activity. Evidently, also other effects indicate different pharmacological properties of nomifensine and cyproheptadine. Nomifensine is thought to be a dopaminergic drug and according to this mechanism induces the locomotor stimulation and the stereotypy [6, 8, 9]. Cyproheptadine is devoid of such properties, thus the dopaminergic mechanism of its anticataleptic (antineuroleptic) activity cannot be taken into account. Thus, the results presented allow us to think that the dopaminergic and cholinolytic mechanisms may be ruled out as the cause of the anticataleptic action of cyproheptadine; however, antiserotonergic and antihista-

minic actions may be involved. Antiserotonin properties of cyproheptadine were mainly found on the periphery [20, 21, 22]. But there are data indicating that cyproheptadine may also exert such an action in the central nervous system [1,10]. Our last experiments on the hind limb flexor reflex of a spinal rat seem to be a further evidence for such an action. We have shown that cyproheptadine prevents the stimulation of this reflex caused by L-5-hydroxytryptophan, L-tryptophan, LSD and fenfluramine [15]. The same results in the flexor reflex test were obtained testing WA-335 [15], another 5-HT blocker [4, 11, 13]. As demonstrated in our other investigations, WA-335 exerts also an antagonistic action on neuroleptic-induced catalepsy but has no influence on pilocarpine and physostigmine-induced catalepsy [17], so the profile of its action is like that of cyproheptadine. This may prove an antiserotonergic mechanism of the anticataleptic action of both compounds. On the other hand, other investigations carried out in this laboratory, showed that two inhibitors of the 5-HT synthesis (p-chlorophenylalanine and p-chloramphetamine) did not influence the catalepsy induced by spiperon and fluphenazine [12,19]. These results are not in accordance with those described by other authors which have found an antagonism of p-chlorophenylalanine towards the catalepsy induced by haloperidol or chlorpromazine [7]. These discrepancies can be caused by the fact that two types of 5-HT neurons, opposite in their function, may exist in the central nervous system. The specific inhibition of the 5-HT neurons, but not general inhibition of 5-HT synthesis, may be helpful to elucidate this point. Such studies are now in progress. Recently it has been shown that lesions of the medial or dorsal raphe nuclei reduce the cataleptic actions of some other neuroleptics, among other that one of fluphenazine studied in the paper presented here [2].

As mentioned before, cyproheptadine possesses antihistaminic properties [20,21]. The results of this paper indicate that the profile of its anticataleptic action is similar but not identical with that of promethazine, which was used here as a standard antihistaminic. WA-335 cited above, causing a similar anticataleptic action, shows not only antiserotonergic but powerful antihistaminic properties as well [4]. Thus, the latter properties also have to be taken into consideration as the cause of the anticataleptic (antineuroleptic) action of cyproheptadine or WA-335.

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