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Antihistamine-monoamine oxidase inhibitor interaction in rabbits

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The ability of a drug to produce a fatal hyperpyrexia in rabbits pretreated with a monoamine oxidase inhibitor (MAOI) may be predictive of a serious clinical drug-drug interaction. These interactions appear to be due to 5-hydroxytryptamine (5-HT) potentiation. Since some antihistamines have been shown to block the neuronal 5-HT uptake, several antihistamines were tested in phenelzine-pretreated rabbits. The alkylamines (dexchlorpheniramine, chlorpheniramine, dexbrompheniramine, brompheniramine and pheniramine) and the ethylenediamines (mepyramine and tripelennamine) were active in producing a fatal hyperpyrexia in the MAOI-pretreated rabbits. Diphenhydramine and triprolidine produced a fatal hyperpyrexia in approximately one half of the animals tested. The mechanism responsible for the interaction between chlorpheniramine, a representative of the active compounds, and phenelzine appears to be 5-HT potentiation. Antihistamines that did not produce a fatal hyperpyrexia in the phenelzine pretreated rabbits were: phenyltoloxamine, promethazine, methdilazine, trimeprazine, meclizine, chlorcyclizine, cyproheptadine, phenindamine and dimethpyrindene. The potential use of the active compounds as antidepressants is also discussed.

Several clinical reports indicate that pethidine or the tricyclic antidepressants, when administered to patients receiving a monoamine oxidase inhibitor (MAOI), may produce severe adverse reactions (Palmer, 1960; Shee, 1960; Davies, 1960; Brachfeld, Wirtshafter & Wolfe, 1963; Stanley & Pal, 1964; Saunders, 1965). The symptoms of such an interaction include hyperexcitability, motor restlessness and hyperpyrexia. Both pethidine and the tricyclic antidepressants have been shown to exhibit similar symptoms culminating in a fatal hyperpyrexia when administered to rabbits pretreated with a monoamine oxidase inhibitor (Nymark & Moller-Neilsen, 1963; Loveless & Maxwell, 1965; Penn & Rogers, 1971; Sinclair, 1972a). Therefore, it appears that the hyperpyrexia response in MAOI pretreated rabbits may be a useful model for predicting similar potentially dangerous interactions with MAOIs.

The ability of pethidine and imipramine to produce a fatal hyperpyrexia in MAOI-pretreated rabbits appears to be due to an exaggerated 5-hydroxytryptamine (5-HT) response (Gong & Rogers, 1971; Sinclair, 1972). Since some antihistamines have been shown to block neuronal 5-HT uptake (Carlsson & Lindqvist, 1969) they may also have the potential for producing a serious adverse reaction in patients being treated with a MAOI. Therefore, several antihistamines were tested in rabbits pretreated with phenelzine.

METHODS

The MAOI used was phenelzine sulphate. The antihistamine test drugs included: chlorpheniramine maleate, dexchlorpheniramine maleate, brompheniramine maleate,

dexbrompheniramine maleate, pheniramine maleate, mepyramine maleate, tripelennamine HCl, diphenhydramine HCl, phenyltoloxamine citrate, promethazine HCl, methdilazine HCl, trimeprazine tartrate, meclizine HCl, chlorcyclizine HCl, triprolidine HCl, cyproheptadine HCl, phenindamine tartrate and dimethpyrindene maleate. Other drugs used included: chlorpromazine HCl, DL-*p*-chlorophenylalanine (PCPA), α-methyl-*p*-tyrosine methyl ester HCl, reserpine and DL-5-hydroxytryptophan (5–HTP). Most test drugs and chlorpromazine were dissolved in normal saline. Due to lack of solubility in saline, meclizine and cyproheptadine were dissolved in a small volume of propylene glycol and diluted with saline, PCPA and reserpine were suspended in propylene glycol and α-methyl-*p*-tyrosine was dissolved in distilled water. Drug doses are expressed in terms of the actual preparations used, in most cases the salt.

New Zealand white rabbits of either sex (1·6–3·2 kg) received phenelzine (30 mg/kg, i.p.) on 2 successive days. On the third day, approximately 42 and 18 h after the MAOI pretreatment, the animals were restrained in stocks and rectal temperatures were recorded at 15 min intervals with the aid of a telethermometer (Yellow Springs Instrument Company). When the temperature of a given rabbit had been stable for 30 min a test drug was slowly administered via a marginal ear vein.

To characterize the hyperpyrexia pharmacologically, chlorpheniramine was selected as a representative of the active compounds. Experiments were made as described above with the addition of one of the following pretreatments: chlorpromazine (5 mg/kg, i.v.) or cyproheptadine (5 mg/kg. i.v.) 30 min before chlorpheniramine; PCPA (125 mg/kg, i.p.) approximately 66, 42, and 18 h before chlorpheniramine; α-methyl-*p*-tyrosine (80 mg/kg, i.p.) 48, 36, 24 and 12 h before chlorpheniramine and reserpine (0·5 mg/kg, i.p.) 42 and 18 h before chlorpheniramine. In addition, chlorpheniramine (5 mg/kg, i.v.) was administered to animals that had been pretreated with 5-HTP (60 mg/kg, i.v.) 1 h earlier.

RESULTS

The effects of the test antihistamines on the rectal temperature of phenelzine-pretreated rabbits are illustrated in Table 1. All agents classified as alkylamines and ethylenediamines produced a rapid onset of motor restlessness, hyperexcitability,

Table 1. *Temperature changes in phenelzine pretreated rabbits after various antihistamines.*

Test drug[a]	Dose mg/kg	Phenelzine[b] 30 mg/kg	Temperature change ± s.e. at times (mins) indicated −15	30	60	120	Hyperpyrexia[c] 3°C	Died
ALKYLAMINES								
Dexchlorpheniramine	2·5	+	0·00 ±0·00	3·05 ±0·24			3/4	4/4
	2·5	−	0·01 ±0·01	0·21 ±0·08	0·24 ±0·09	0·21 ±0·08	0/4	0/4
	10	−	−0·04 ±0·02	0·84 ±0·12	0·48 ±0·14	0·45 ±0·12	0/4	0/4
Chlorpheniramine	5	+	0·02 ±0·02	3·38 ±0·33			4/4	4/4
	5	−	0·03 ±0·04	0·41 ±0·08	0·65 ±0·08	0·70 ±0·11	0/4	0/4
	10	−	−0·01 ±0·01	0·74 ±0·28	0·85 ±0·26	0·75 ±0·24	0/4	0/4

Table 1—*continued*

Dexbrompheniramine	5	+	0·00 ±0·00	3·78 ±0·24			4/4	4/4
	5	−	−0·01 ±0·01	0·34 ±0·23	0·61 ±0·19	0·74 ±0·14	0/4	0/4
	10	−	−0·03 ±0·01	0·85 ±0·29	1·13 ±0·42	1·76 ±0·68	2/4	2/4
Brompheniramine	5	+	0·01 ±0·01	3·50 ±0·32			3/4	4/4
	5	−	−0·01 ±0·01	0·33 ±0·15	0·51 ±0·11	0·45 ±0·11	0/4	0/4
	10	−	−0·01 ±0·01	1·03 ±0·16	1·09 ±0·24	1·33 ±0·81	1/4	1/4
Pheniramine	5	+	0·00 ±0·00	2·66 ±0·46	2·97 ±0·91	1·28 ±0·97	2/4	2/4
	10	+	0·04 ±0·02	3·08 ±0·22	4·53 ±0·41		4/4	4/4
	10	−	0·03 ±0·03	0·80 ±0·14	0·64 ±0·29	0·44 ±0·35	0/4	0/4
ETHYLENEDIAMINES								
Mepyramine	5	+	−0·03 ±0·12	2·79 ±0·44	4·26 ±0·32		4/4	4/4
	5	−	0·01 ±0·01	0·20 ±0·10	−0·13 ±0·15	−0·38 ±0·14	0/4	0/4
	10	−	−0·10 ±0·10	0·35 ±0·24	0·15 ±0·24	0·00 ±0·06	0/4	0/4
Tripelennamine	5	+	0·01 ±0·01	2·98 ±0·28	4·20 ±0·30		3/4	4/4
	5	−	0·06 ±0·02	1·43 ±0·13	1·59 ±0·12	1·31 ±0·23	0/4	0/4
ETHANOLAMINES								
Diphenhydramine	10	+	0·01 ±0·00	1·02 ±0·28	1·45 ±0·54		4/8	4/8
	10	−	0·01 ±0·01	0·33 ±0·10	0·21 ±0·22	0·24 ±0·31	0/4	0/4
Phenyltoloxamine	10	+	−0·01 ±0·01	0·19 ±0·44	0·03 ±0·40	−0·36 ±0·36	0/4	0/4
PHENOTHIAZINES								
Promethazine	10	+	0·01 ±0·01	−1·54 ±0·37	−2·40 ±0·62	−3·19 ±0·74	0/4	0/4
Methdilazine	10	+	−0·03 ±0·04	−0·78 ±0·32	−1·17 ±0·49	−2·12 ±0·63	0/4	1/4
Trimeprazine	10	+	0·00 ±0·03	−0·90 ±0·16	−1·56 ±0·21	−2·43 ±0·21	0/4	0/4
PIPERAZINES								
Meclizine	10	+	0·00 ±0·00	0·15 ±0·28	0·08 ±0·29	−0·14 ±0·23	0/4	0/4
Chlorcyclizine	10	+	0·00 ±0·03	−0·74 ±0·11	−0·84 ±0·09	−0·65 ±0·14	0/4	0/4
MISCELLANEOUS								
Triprolidine	10	+	0·01 ±0·01	2·39 ±0·30	2·80 ±0·43	1·28 ±0·29	2/4	1/4
	10	−	0·00 ±0·00	0·48 ±0·07	−0·05 ±0·12	−0·23 ±0·12	0/4	0/4
Cyproheptadine	5	+	−0·04 ±0·02	−0·53 ±0·13	−0·65 ±0·26	−0·80 ±0·34	0/4	0/4
Phenindamine	10	+	0·00 ±0·04	−0·51 ±0·04	−0·59 ±0·23	0·06 ±0·45	0/4	0/4
Dimethpyrindene	10	+	0·00 ±0·03	−0·04 ±0·17	−0·18 ±0·14	−0·03 ±0·17	0/4	0/4

a. Administered i.v. at time zero.
b. Administered i.p. 42 and 18 h before temperature recording.
c. Number developing hyperpyrexia of 3°/number tested.

shivering-like tremors, tachypnea and hyperpyrexia which culminated in death of the animals. Most of these compounds at doses of 5 mg/kg resulted in death of the phenelzine-pretreated animals within 75 min of injection. Dexchlorpheniramine at this dose however, produced death in 3 of the 4 animals tested within 30 min of injection and before a hyperpyrexia of 3° was reached. Lowering the dose of dexchlorpheniramine to 2·5 mg/kg prolonged the time until death after injection in all but 1 animal. Pheniramine on the other hand, was inconsistent at a dose of 5 mg/kg in MAOI-pretreated animals. Only 2 of the 4 animals tested reached a fatal hyperpyrexia of 3°. Increasing the dose to 10 mg/kg consistently produced death after a marked elevation in temperature.

In the present study, as previously found (Loveless & Maxwell, 1965; Sinclair, 1972), there was a good correlation between a hyperpyrexia of 3° and death of the animal.

Of the other antihistamines that were tested at doses of 10 mg/kg in phenelzine-pretreated animals, only diphenhydramine and triprolidine showed any activity. Approximately one half of these animals exhibited hyperpyrexia and died. Cyproheptadine was inactive at doses of 5 mg/kg and produced a fatal respiratory depression at doses of 10 mg/kg in phenelzine-pretreated animals.

Most of the compounds that produced marked hyperpyrexia when administered to MAOI-pretreated animals, produced only a slight increase in temperature when administered to non-pretreated animals. However, some of the animals given dexbrompheniramine (10 mg/kg), brompheniramine (10 mg/kg) or tripelennamine (5 mg/kg) exhibited a substantial elevation of temperature (Table 1). Their behaviour resembled that seen when these drugs were administered to MAOI pretreated animals, although few of the non-pretreated animals died.

A number of agents that alter the level or activity of biogenic amines in the brain were tested on the phenelzine-chlorpheniramine interaction. The agents chlorpromazine (5 mg/kg) and cyproheptadine (5 mg/kg), which are known to antagonize 5-HT, both partially antagonized the development of the interaction (Fig. 1). Only 4 of the 9 animals pretreated with chlorpromazine in addition to the MAOI developed a fatal hyperpyrexia of 3° after chlorpheniramine (5 mg/kg). None of the 4 animals

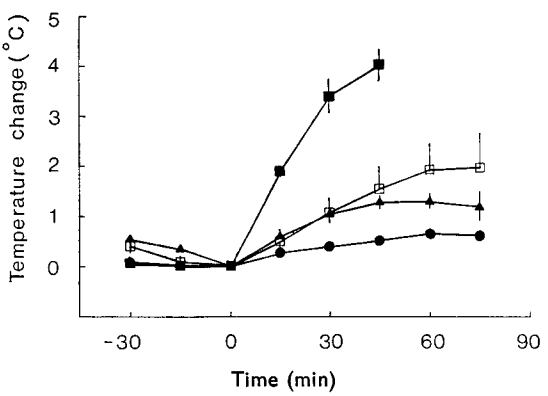

FIG. 1. The chlorpheniramine-phenelzine interaction and its antagonism as measured by rectal temperature changes in rabbits. Chlorpheniramine (5 mg/kg) was administered at time zero in all curves. In addition, phenelzine (30 mg/kg) was administered 42 and 18 h before the test in all curves except (●). Chlorpromazine (5 mg/kg) (□) and cyproheptadine (5 kg/kg) (▲) were administered at time −30 min. Each point represents the mean ±s.e. for 4 animals except in curve (□) where 9 animals were used.

pretreated with cyproheptadine developed a hyperpyrexia of 3° during the MAOI — chlorpheniramine interaction although one animal died after a rise of 2·15°. Neither α-methyl-*p*-tyrosine nor reserpine protected the animals from a fatal hyperpyrexic phenelzine—chlorpheniramine interaction. However, after pretreatment with PCPA only 1 of the 5 animals developed a 3° rise in temperature during the MAOI-chlorpheniramine interaction although 2 of the rabbits died (Fig. 2). The 5-HT precursor,

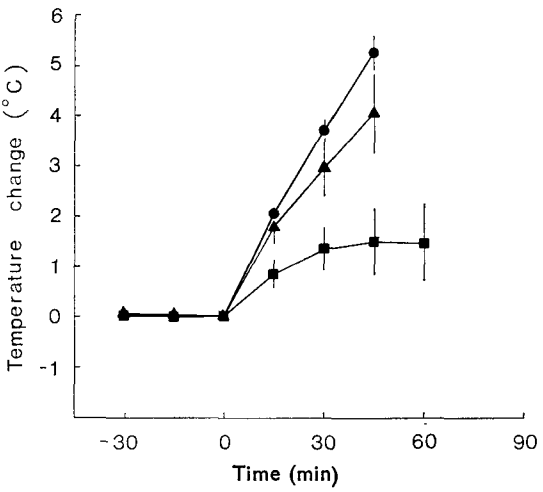

FIG. 2. The effects of PCPA, α-methyl-*p*-tyrosine and reserpine on the chlorpheniramine-phenelzine interaction. In all curves phenelzine (30 mg/kg) was administered 42 and 18 h before the test and chlorpheniramine (5 mg/kg) was administered at time zero. In addition, the following drugs were administered at the times indicated: ●, α-methyl-*p*-tyrosine (80 mg/kg) 48, 36, 24 and 12 h before the test, n = 4; ▲ reserpine (0·5 mg/kg) 42 and 18 h before the test, n = 5; and ■ PCPA (125 mg/kg) 66, 42 and 18 h before the test, n = 5. Each point on the curve represents the mean ± s.e.

5-HTP (60 mg/kg), produced a slight rise in the rectal temperature of non-pretreated rabbits. This elevation of temperature was potentiated in all animals when chlorpheniramine (5 mg/kg) was administered 1 h after the 5-HTP (Fig. 3). This potentiation proved fatal to 6 of the 7 animals studied.

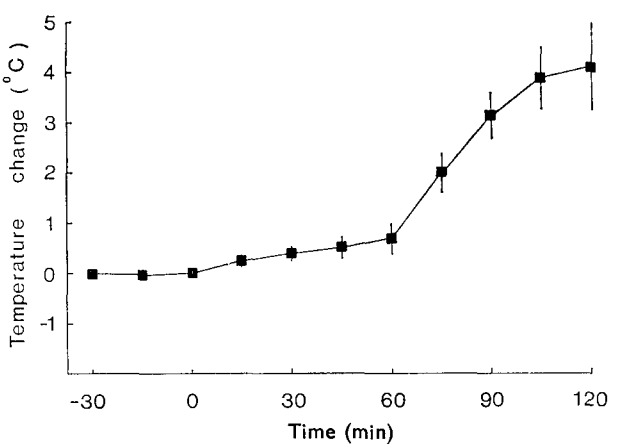

FIG. 3. 5-HTP potentiation by chlorpheniramine. 5-HTP (60 mg/kg) was administered at time zero followed by chlorpheniramine (5 mg/kg) at time 60 min. Each point represents the mean ± s.e. for 7 animals.

DISCUSSION

The finding that certain antihistamines, particularly the alkylamines and ethylenediamines, produced a fatal interaction with a MAOI in rabbits suggests that they have the potential for exerting a serious interaction with MAOI's in man. However, the literature lacks reports of any such reactions occurring between such drug combinations in man. This may be due to the fact that a number of the active antihistamines are generally used in low doses for antihistamine activity. Higher doses may be required to produce an interaction in subjects receiving a MAOI. It might be expected that the antihistamines, mepyramine and tripelennamine, which are used in relatively high doses, possess the greater potential for producing an adverse drug interaction in patients being treated with a MAOI.

The symptoms of the interaction between certain antihistamines and phenelzine are the same as those seen when pethidine (Sinclair, 1972a). ethoheptazine (Sinclair, 1972b) or the tricyclic antidepressants (Loveless & Maxwell, 1965; Sinclair, unpublished observations) are administered to MAOI-pretreated rabbits. This observation suggests a common mode of action. Evidence has been presented indicating that pethidine (Sinclair, 1972a), imipramine (Gong & Rogers, 1971) and ethoheptazine (Sinclair, 1972b) exert their effects by potentiating 5-HT in MAOI-pretreated animals.

The following evidence supports a similar mechanism of action for chlorpheniramine in the interaction with phenelzine: (1) pretreatment with a 5-HT antagonist, chlorpromazine or cyproheptadine, partially antagonized the development of the interaction; (2) the tryptophan hydroxylase inhibitor, PCPA, also partially antagonized the development of the interaction; (3) pretreatment with reserpine or the tyrosine hydroxylase inhibitor, α-methyl-*p*-tyrosine, did not alter the chlorpheniramine–phenelzine interaction; (4) chlorpheniramine potentiates the hyperpyrexia produced by 5-HTP; and (5) Carlsson & Lindqvist (1969) and Lidbrink, Jonsson & Fuxe (1971) found that chlorpheniramine was very effective in blocking neuronal 5-HT uptake. The doses and pretreatment schedules for PCPA, reserpine and α-methyl-*p*-tyrosine were the same as those used by Gong & Rogers (1971). These investigators found that PCPA prevented the MAOI from increasing the brain levels of 5-HT without altering the normal increase in catecholamines whereas reserpine and α-methyl-*p*-tyrosine had the opposite effects.

It is interesting that most of the active antihistamines in this study are also effective in blocking neuronal noradrenaline uptake or enhancing the actions of noradrenaline (Isaac & Goth, 1967; McNeill & Brody, 1968; Lidbrink & others, 1971; Barnett, Taber & Roth, 1969.) An exception is mepyramine which induces a fatal hyperpyrexia in phenelzine-pretreated rabbits but does not block catecholamine uptake in adrenergic nerve terminals (Isaac & Goth, 1967). On the other hand, phenindamine which blocks noradrenaline neuronal uptake (Isaac & Goth, 1967; McNeill & Brody, 1968) was inactive in the present study.

The tricyclic antidepressants block noradrenaline and 5-HT uptake (Hertting, Axelrod & Whitby, 1961; Axelrod & Inscoe, 1963; Blackburn, French & Merrills, 1967). More recently it has been reported that the tertiary tricyclic agents such as imipramine and amitriptyline preferentially block 5-HT uptake whereas the secondary agents such as desipramine and nortriptyline preferentially block noradrenaline uptake (Carlsson, Fuxe & Ungerstedt, 1968; Fuxe & Ungerstedt, 1968; Carlsson, Corrodi & others, 1969a, b). If 5-HT potentiation is an important property of the

tricyclic antidepressants in relieving depression, then the active antihistamines in this study should be useful antidepressants. Lidbrink & others (1971) cite evidence favouring the involvement of 5-HT in mood-elevation and noradrenaline in psychomotor activation. They further suggest that since the antihistamines chlorpheniramine and brompheniramine are potent compounds in blocking both 5-HT and noradrenaline uptake, they may be useful in certain types of depression. A paucity of information is available with regard to the use of antihistamines as antidepressants. Hankoff, Grundlach & others (1964) concluded that diphenhydramine was ineffective as an antidepressant. However, a re-evaluation of their data by Barnett & others (1969), revealed that 10 of the 13 depressed patients showed significant improvement.

In summary, a number of alkylamine and ethylenediamine antihistamines appear to have the potential for producing a serious adverse reaction in patients being treated with a MAOI. Furthermore, if 5-HT potentiation is important in the relief of depression, these antihistamines may also be useful antidepressants.

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