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Dextromethorphan-monoamine oxidase inhibitor interaction in rabbits

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Severe toxic reactions may occur clinically when imipramine, pethidine or dextromethorphan is administered to a patient being treated with a monoamine oxidase inhibitor (MAOI). Previous reports indicate that imipramine or pethidine produces symptoms characterized by motor restlessness, tremor, extreme hyperpyrexia and death when administered to phenelzine-pretreated rabbits. The present study shows that dextromethorphan (5 mg kg^{-1}) produces identical symptoms in rabbits pretreated with phenelzine sulphate (30 mg kg^{-1}) or nialamide HCl (50 mg kg^{-1}) 42 and 18 h before temperature recording. The dextromethorphan-MAOI interaction appears to be due to a 5-hydroxytryptamine potentiation. In the unanaesthetized cat nictitating membrane preparation, dextromethorphan (5 mg kg^{-1}) markedly enhanced the response of noradrenaline and 5-HT but antagonized the effects of tyramine. This suggests that dextromethorphan blocks the uptake of these amines in the adrenergic nerve endings.

Recently two fatalities have been reported following the ingestion of large doses of a cough preparation containing dextromethorphan by patients being treated with the monoamine oxidase inhibitor (MAOI) phenelzine (Rivers & Horner, 1970; Shamsie & Barriga, 1971). The symptoms reported included extreme hyperpyrexia, restlessness and dilated pupils; symptoms identical with those occurring as a result of an adverse interaction between pethidine or the tricyclic antidepressants and an MAOI (Palmer, 1960; Shee, 1960; Davies, 1960; Brachfeld, Wirtshafter & Wolfe, 1963; Stanley & Pal, 1964; Saunders, 1965). Rabbits, pretreated with a MAOI, exhibit similar symptoms culminating in a fatal hyperpyrexia upon injection of pethidine or a tricyclic antidepressant (Nymark & Moller-Nielsen, 1963; Loveless & Maxwell, 1965; Penn & Rogers, 1971; Sinclair, 1972a). Therefore, the present study was undertaken to examine the effects of dextromethorphan in MAOI-pretreated rabbits with the hope of providing information on the mechanism responsible for the interaction.

METHODS

Rabbit interaction

Pretreatment schedules were arranged to allow temperature recordings to be made on 4 animals on any given day. New Zealand white rabbits of either sex (1·6–2·8 kg) were treated with phenelzine sulphate (30 mg kg^{-1}, i.p.), pargyline HCl (40 mg kg^{-1}, i.p.) or nialamide HCl (50 mg kg^{-1}, i.p.) on 2 successive days. The following day, the animals were restrained in stocks and rectal temperatures were recorded at 15 min intervals using thermistor probes. When the temperature of a given rabbit had been stable for 30 min, dextromethorphan (5 mg kg^{-1}) was slowly administered via a marginal ear vein. The experiments were made at 20–21°.

The experiments were repeated in phenelzine-pretreated animals with the addition of one of the following pretreatments: 5 mg kg^{-1}, i.v. chlorpromazine HCl or cyproheptadine HCl 30 min before dextromethorphan; 125 mg kg^{-1}, i.p. (±)-*p*-chlorophenylalanine (PCPA) 66, 42 and 18 h before dextromethorphan and 80 mg kg^{-1}, i.p. α-methyl-*p*-tyrosine 48, 36, 24 and 12 h before dextromethorphan. Finally, 5 mg kg^{-1}, i.v. dextromethorphan was administered to rabbits pretreated 1 h earlier with 60 mg kg^{-1}, i.v. 5-hydroxytryptophan (5-HTP).

Cat nictitating membrane

The unanaesthetized cat nictitating membrane preparation was prepared as previously described (Sinclair, 1973). Cannulas for intravenous drug administration were placed in both femoral and cephalic veins. Two control responses were obtained for 20 μg kg^{-1} 5-hydroxytryptamine creatinine sulphate (5-HT), 10 μg kg^{-1} noradrenaline HCl and 0·5 mg kg^{-1} tyramine HCl. Doses are expressed as the free base for 5-HT and noradrenaline and as the salt for tyramine. Each drug was administered in 15 s through a separate cannula using a Harvard infusion pump. Injections were administered in a random order and the order was reversed to obtain the second control response. After each injection the heart rate and blood pressure were allowed to return to normal before another drug was administered. Dextromethorphan (5 mg kg^{-1}) was then administered through the fourth cannula and the injections of noradrenaline, 5-HT and tyramine were repeated.

RESULTS

Rabbit interaction

Dextromethorphan (5 mg kg^{-1}) produced motor restlessness, shivering-like tremors, hyperexcitability, dilated pupils, tachypnoea and hyperpyrexia in phenelzine-pretreated rabbits (Fig. 1). Five of the seven rabbits tested died within 1 h of being given

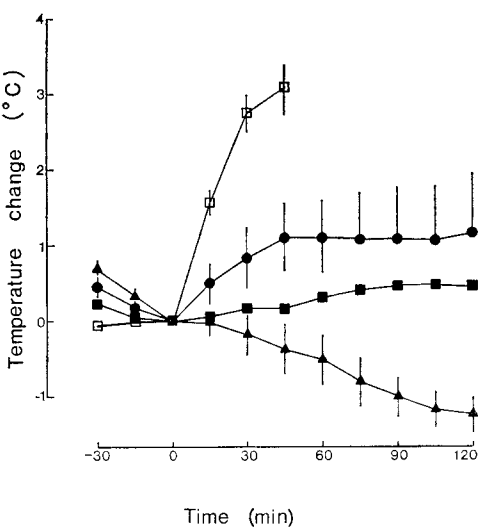

FIG. 1. The dextromethorphan-phenelzine interaction and its antagonism as measured by recta temperature changes in rabbits. Dextromethorphan (5 mg kg^{-1}) was administered at time zero in all curves. In addition, phenelzine (30 mg kg^{-1}) was administered 42 and 18 h before the test in all curves except (■). Chlorpromazine (5 mg kg^{-1}) (▲) and cyproheptadine (5 mg kg^{-1}) (●) were administered at time −30 min. Each point represents the mean ± s.e. for 4 animals except curve □, where 7 were used.

dextromethorphan. The same dose in non-pretreated rabbits produced none of the above-mentioned signs. A lower dose of 3 mg kg^{-1} dextromethorphan produced similar but generally less intense symptoms of the interaction in phenelzine-pretreated rabbits. Only one of the four rabbits tested at this dose exhibited a 3° temperature increase and death.

Dextromethorphan was shown to be capable of producing this interaction in rabbits pretreated with other MAOI's. Animals pretreated with pargyline succumbed to the interaction when challenged with dextromethorphan less consistently than did phenelzine-pretreated animals. At 1 h after dextromethorphan injection, the mean temperature increase in pargyline-pretreated animals was 0·38 ± 0·48° and 2 animals died of the seven tested. On the other hand, nialamide-pretreated rabbits developed intense symptoms of the interaction when dextromethorphan was administered. The mean temperature increase in these animals at 1 h was 3·78 ± 0·03° and all four animals died.

The dextromethorphan-phenelzine interaction in rabbits was completely prevented by the administration of chlorpromazine before dextromethorphan and partially blocked by a similar administration of cyproheptadine (Fig. 1). All four chlorpromazine-pretreated animals survived whereas one of the four cyproheptadine-pretreated animals died. Pretreatment with the tryptophan hydroxylase inhibitor, PCPA, also prevented the dextromethorphan-phenelzine interaction. This was not the case when the tyrosine hydroxylase inhibitor, α-methyl-*p*-tyrosine, was used (Fig. 2).

The precursor of 5-HT, 5-HTP, when administered to rabbits in doses of 75–100 mg kg^{-1} produces hyperpyrexia and symptoms which resemble the dextromethorphan-MAOI interaction (Horita & Gogerty, 1958; Loew & Taeschler, 1966) which suggests a 5-HT involvement in the interaction. A smaller dose of 5-HTP, 60 mg kg^{-1},

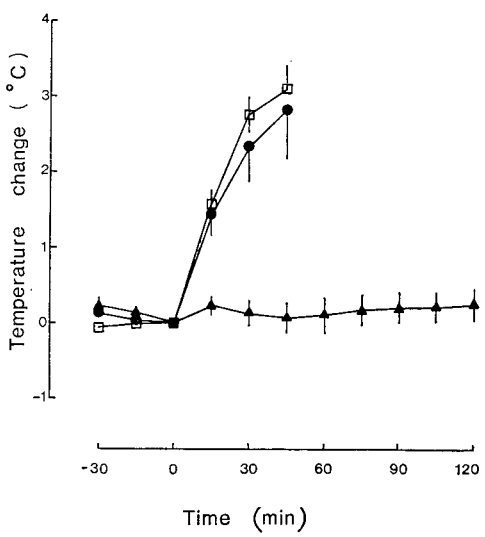

FIG. 2. The effects of PCPA and α-methyl-*p*-tyrosine on the dextromethorphan-phenelzine interaction. □, same curve as in Fig. 1. In all curves phenelzine (30 mg kg^{-1}) was administered 42 and 18 h before the test and dextromethorphan (5 mg kg^{-1}) was administered at time zero. In addition, the following drugs were administered at the times indicated: ▲, PCPA (125 mg kg^{-1}) 66, 42 and 18 h before the test, n = 6; and ●, α-methyl-*p*-tyrosine (80 mg kg^{-1}) 48, 36, 24 and 12 h before the test, n = 8.

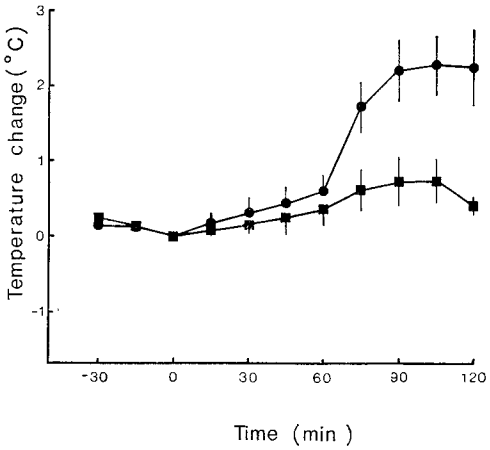

FIG. 3. 5-HTP potentiation by dextromethorphan. The animals represented in both curves received 5-HTP (60 mg kg^{-1}) at time zero. In addition, dextromethorphan (5 mg kg^{-1}) was injected at time 60 min in curve ●. Each point represents the mean ± s.e. for 8 animals.

produced little or no temperature change in non-pretreated animals. However, when these animals received dextromethorphan (5 mg kg^{-1}) 1 h after the 5-HTP, there was a definite elevation of the rectal temperatures (Fig. 3).

Cat nictitating membrane

The tricyclic antidepressants and pethidine, which produce an interaction with MAOI's that is indistinguishable from that of the dextromethorphan-MAOI interaction, are known to block the neuronal uptake of noradrenaline and 5-HT (Carlsson, Corrodi & others, 1969; Carlsson, Jonason & Lindqvist, 1969; Carlsson & Lindqvist, 1969). Drugs which block noradrenaline and 5-HT uptake have been shown to enhance the effects of noradrenaline and 5-HT but to antagonize the effects of tyramine on the cat nictitating membrane (Trendelenburg, 1959; Sigg, Soffer & Gyermek, 1963; Wakade, Kanwar & Gulati, 1970). In the present study dextromethorphan also markedly enhanced the responses to noradrenaline (260 ± 43%) and 5-HT (% of control = 203 ± 18 s.e., n = 4) and antagonized the effects of tyramine (72 ± 8%) suggesting that dextromethorphan also blocks neuronal uptake of these amines.

DISCUSSION

Reports have appeared showing that pethidine, the tricyclic antidepressants or dextromethorphan may produce a serious adverse drug interaction when administered to patients receiving a MAOI. Pethidine and the tricyclic antidepressants have also been shown to produce marked hyperpyrexia and death when administered to rabbits pretreated with a MAOI. The finding, in the present study, that dextromethorphan produces a similar interaction in rabbits supports the suggestion that this test is useful for predicting clinically significant adverse drug interactions (Sinclair, 1972 b,c).

Some of the symptoms of the interaction between pethidine, the tricyclic antidepressants or dextromethorphan and a MAOI in man; e.g., motor restlessness, hyperexcitability and hyperpyrexia, are the same as those that occur in the rabbit. This suggests that the mechanism responsible for the interaction may be similar in man and the rabbit.

It has been reported that the interaction between pethidine or the tricyclic antidepressants and a MAOI in rabbits is likely due to an enhanced 5-HT response (Gong & Rogers, 1971; Sinclair, 1972a). The following evidence supports a similar mechanism of action for the dextromethorphan-MAOI interaction: pretreatment with the tryptophan hydroxylase inhibitor, PCPA, antagonized the development of the interaction, whereas, pretreatment with the tyrosine hydroxylase inhibitor, α-methyl-*p*-tyrosine, did not alter the dextromethorphan-MAOI interaction; pretreatment with the 5-HT antagonists, chlorpromazine or cyproheptadine, antagonized the development of the interaction; and dextromethorphan enhanced the slight elevation in temperature produced by 5-HTP (60 mg kg^{-1}). The doses and pretreatment schedules for PCPA and α-methyl-*p*-tyrosine were the same as those used by Gong & Rogers (1971). These authors reported that PCPA prevented the MAOI from increasing the brain levels of 5-HT in rabbits without altering the normal increase in catecholamines, whereas, α-methyl-*p*-tyrosine had the opposite effects.

The neuronal uptake blocking action of dextromethorphan was tested using the unanaesthetized cat nictitating membrane preparation. Wakade & others (1970) have shown that the nictitating membrane exhibits denervation supersensitivity to 5-HT and that 5-HT responses are enhanced by cocaine. They, therefore, proposed that 5-HT is taken up by adrenergic nerve endings.

Neuronal uptake blocking agents, cocaine and imipramine, have been shown to enhance the cat nictitating membrane responses to noradrenaline and 5-HT (Trendelenburg, 1959; Sigg & others, 1963; Wakade & others, 1970). However, cocaine antagonizes the effects of tyramine and other indirectly acting amines on this preparation (Trendelenburg, 1959, 1961; Ryall, 1961; Fleckenstein & Stockle, 1955). Presumably these actions are due to the blocking of a common uptake system (Trendelenburg, 1961; Furchgott, Kirpekar & others, 1963; Johnson & Kahn, 1966). Our finding that dextromethorphan enhanced the responses of noradrenaline and 5-HT but antagonized the effects of tyramine on the cat nictitating membrane suggests that dextromethorphan also blocks neuronal uptake of these amines. Such a mechanism would be consistent with the finding that the tricyclic antidepressants, pethidine and certain antihistamines all block 5-HT uptake (Carlsson & others, 1969; Carlsson, Jonason & Lindqvist 1969; Carlsson & Lindqvist, 1969) and all exhibit a characteristic interaction in MAOI-pretreated rabbits (Nymark & Moller-Nielsen, 1963; Loveless & Maxwell, 1965; Penn & Rogers, 1971; Sinclair 1972 a, b).

The site of action of 5-HT in temperature regulation in the rabbit has not been established. A careful study by Jacob, Girault & Peindaries (1972) in which 5-HTP and two salts of 5-HT were administered by various routes, doses and techniques revealed that the effects of these agents on temperature in the conscious rabbit were mainly dose-dependent. Low doses produced an initial hypothermia as was previously shown by Cooper, Cranston & Honour (1965) and Bligh, Cottle & Maskrey (1971), whereas, higher doses produce hyperthermia. Although 5-HT in the anterior hypothalamus has been implicated in hyperthermia of cats (Feldberg & Myers, 1965), direct injection of 5-HT into the anterior hypothalamus of the rabbit was ineffective (Cooper & others, 1965).

It is interesting that the (−)-isomer of dextromethorphan, levorphanol, as well as codeine do not produce the characteristic hyperpyrexia interaction in MAOI-pretreated rabbits (Sinclair, 1972b).

The interactions of the tricyclic antidepressants, pethidine or dextromethorphan

with MAOI's appear to be very similar. Chlorpromazine has been used successfully in the clinical treatment of the imipramine-MAOI (Grantham, Neel & Brown, 1964; Saunders, 1965) and pethidine-MAOI (Papp & Benaim, 1958) interactions. Thus, chlorpromazine may well be a useful antagonist of a dextromethorphan-MAOI interaction.

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