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# Interaction between histamine and monoamine oxidase inhibitors

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The monoamine oxidase inhibitors tranylcypromine, nialamide and iproniazid potentiated the actions of histamine on the blood pressure of the cat and on the tracheo-bronchial muscle of the guinea-pig. These findings may have relevance to side-effects of treatment with monoamine oxidase inhibitors.

It is well known that interactions occur between monoamine oxidase inhibitors and other drugs or pharmacologically active substances in foodstuffs. Much of the literature on this topic is concerned with the presence of tyramine in foodstuffs and with other sympathomimetic drugs (Blackwell & Marley, 1964). The most common clinical effects resulting from interaction of these substances with monoamine oxidase inhibitors are hypertension and headache. However, several cases have been reported where headache without concurrent hypertension has occurred in patients on monoamine oxidase inhibitors after eating certain foodstuffs (Horwitz, Lovenberg & others, 1964; Rondell, 1967). It has been suggested, on the basis of animal experiments and clinical observations, that potentiation of the actions of histamine by monoamine oxidase inhibitors may explain the occurrence of headache and other symptoms that could be caused by histamine (Blackwell, Morley & Ryle, 1964; Blackwell, Marley & Mabbitt, 1965; Keele, 1966; Cooper, 1967). We have investigated the effects of some monoamine oxidase inhibitors on cardiovascular responses to histamine in anaesthetized cats, and bronchoconstrictor responses to histamine in anaesthetized guinea-pigs.

## EXPERIMENTAL

Cats of either sex and of 2–4 kg were anaesthetized with chloralose (100 mg/kg) dissolved in normal saline and injected peritoneally. Blood pressure was measured from the femoral artery with an ether pressure transducer and recorded on a Gilson Polygraph. Heart rate was also recorded using a cardiotachometer coupler connected to electrocardiogram electrodes. Drugs were injected into a femoral vein.

Guinea-pigs, approximately 700 g, were anaesthetized with chloralose (20 mg/kg) in 25% urethane; 2 ml/kg was given intraperitoneally. The effects of drugs on tracheo-bronchial smooth muscle were observed using the methods described by McCulloch, Proctor & Rand (1967).

Nialamide (50–100 mg/kg) and iproniazid (50–100 mg/kg) were used as represenatatives of the hydrazine group of monoamine oxidase inhibitors, and tranylcypromine (20 mg/kg) as a representative of the non-hydrazine group. These doses produced marked potentiation of cardiovascular responses to tyramine and amphetamine (Rand & Trinker, 1968).

## RESULTS

In experiments on cats, the responses to a range of doses of histamine were obtained. Then, one of the monoamine oxidase inhibitors was given in a single intravenous injection. In some experiments, half-hourly injections of a single dose of histamine were given to follow the rate of change of the response. The first sign of potentiation of the depressor action of histamine was seen after about 1 h and maximal potentiation occurred about 4 h after injection of monoamine oxidase inhibitors. In all experiments, the responses to doses of histamine were determined again 4 h after the monoamine oxidase inhibitors.

A marked pressor response was observed on intravenous administration of tranylcypromine. The sympathomimetic activity of this drug on the cardiovascular system has been described previously (McCulloch, Trinker & others, 1967). However, this effect wore off and the blood pressure had returned to its control level before 4 h had elapsed.

A marked potentiation of the depressor action of histamine was observed in ten out of the 14 cats treated with a monoamine oxidase inhibitor. The potentiation was greatest after tranylcypromine and least after nialamide. Blackwell, Marley & Taylor (1965) reported that some of the actions of histamine in the cat were potentiated by the monoamine oxidase inhibitor mebanazine, but they gave no details.

The potentiation of depressor responses to histamine in doses ranging from 0·001 to 1·0 $\mu$g/kg by tranylcypromine (20 mg/kg) is shown in Fig. 1. Both the extent and the duration of the depressor response to each dose was increased. The increase in potency of histamine caused by tranylcypromine in this experiment, as estimated from the dose-response curves, was approximately 300-fold.

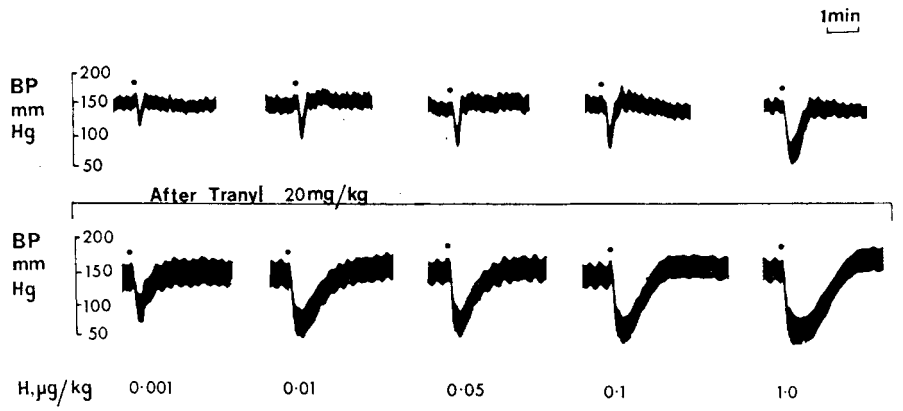


FIG. 1. Records of blood pressure in an anaesthetized cat, 2·4 kg. Histamine was injected intravenously at the points indicated by the dot above each record. The doses are indicated below the records. The upper records were obtained before tranylcypromine. The lower records, obtained 4 h after tranylcypromine, show marked potentiation of the depressor responses to histamine.

The effect of histamine on blood pressure is not always a simple decrease: a biphasic effect consisting of a fall followed by a rise may be seen (for example, in Fig. 3). The secondary pressor response is due to the release of catecholamines, largely from the adrenal medulla, by histamine (Trendelenburg, 1954). In some experiments tranylcypromine not only potentiated the depressor action of histamine,

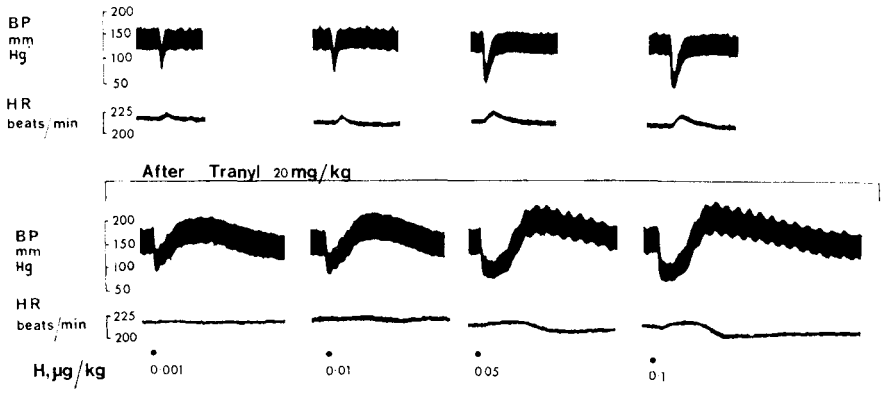


FIG. 2. Records of blood pressure and heart rate in an anaesthetized cat weighing 4·4 kg. 4 h after tranylcypromine, the depressor effect of histamine was enhanced and a secondary pressor phase appeared in the response. Changes in heart rate are in the opposite direction to changes in blood pressure, suggesting they were reflexly induced. Time scale as in Fig. 3.

but also caused the appearance of a secondary pressor effect (see Fig. 2). Tranylcypromine does not potentiate the effects of catecholamines on the cardiovascular system; in fact, it reduces them slightly (Trinker, Fearn & others, 1967; Rand & Trinker, 1968). The appearance of the secondary pressor effect of histamine after tranylcypromine, as shown in Fig. 2, indicates therefore that there was a much increased output of catecholamines.

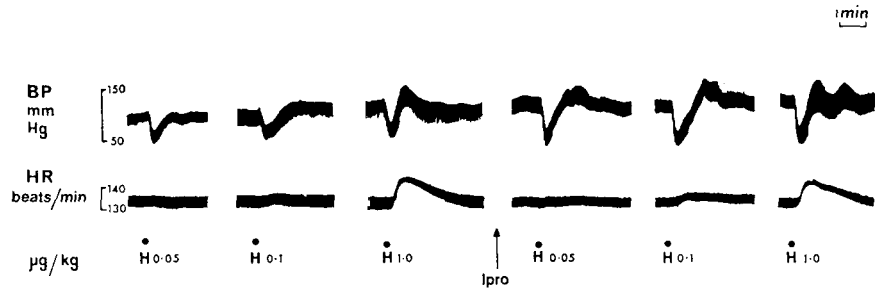


FIG. 3. Records of blood pressure and heart rate in an anaesthetized cat, 2·3 kg. At Ipro, iproniazid (50 mg/kg) was injected intravenously and 4 h later the effects of histamine on the blood pressure were enhanced.

In an experiment with iproniazid (Fig. 3), the control responses to the higher doses of histamine are biphasic. Iproniazid caused increases both in the depressor and pressor phases of the responses.

Histamine produced only slight changes in heart rate and these were not greatly affected by monoamine oxidase inhibitors. The results in Figs 2 and 3 are compatible with the suggestion that changes in heart rate were reflexly induced by the changes in blood pressure.

On account of the complex nature of the action of histamine on the cat blood pressure, and the qualitative change in the response sometimes seen after monoamine oxidase inhibitors, quantitative expression of the results in terms of dose-response is difficult and involves oversimplification of the findings. The results from one experiment in which there was a purely depressor response to histamine both before

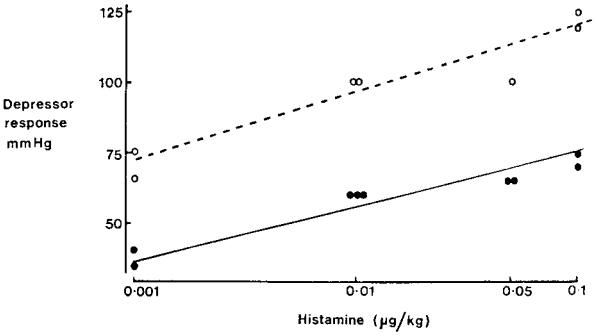


FIG. 4. Log dose-response lines for histamine before and 4 h after 20 mg/kg tranylcypromine in a 2·4 kg cat. The response was the maximal fall in blood pressure from immediately before each injection of histamine. The lines are the calculated regressions. Before tranylcypromine, ● and ——; after tranylcypromine, ○ and ----. Analysis of variance showed that each regression line is significant and they do not differ significantly from parallel. In this experiment there was a 76-fold increase in sensitivity to histamine.

and after tranylcypromine are expressed graphically in Fig. 4, and these data were analysed statistically (see legend).

Bronchospasm produced by histamine in guinea-pigs was enhanced by iproniazid (Fig. 5) or tranylcypromine. The depressor response to histamine in the guinea-pig was not increased by iproniazid (Fig. 5). In contrast, monoamine oxidase inhibitors reduced histamine-induced bronchospasm in the cat although the effects of histamine on blood pressure were markedly enhanced (Fig. 6).

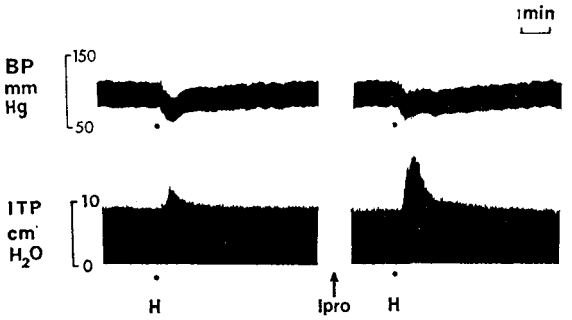


FIG. 5. Records of blood pressure (upper record) and intratracheal pressure (lower record) in an anaesthetized guinea-pig 700 g. At H, histamine was injected intravenously in a dose of 1 mg. At Ipro, iproniazid (50 mg/kg) was injected intravenously, and 4 h later the effect of histamine on intratracheal pressure, but not on blood pressure, was enhanced.

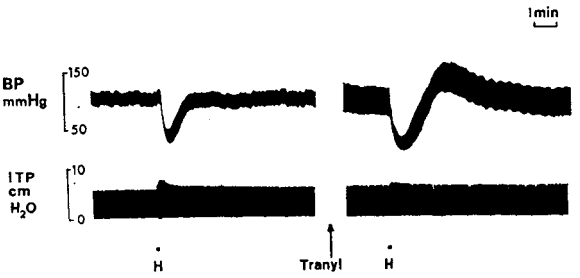


FIG. 6. Records as in Fig. 4, but in an anaesthetized cat, 2·3 kg. At H, histamine (2·5 μg) was injected. At Tranyl, tranylcypromine (20 mg/kg) was injected. 4 h later, the effect of histamine on blood pressure was enhanced, but the effect on intratracheal pressure was reduced.

## DISCUSSION

The potentiation by monoamine oxidase inhibitors of the actions of histamine is probably due to impairment of metabolic inactivation. Monoamine oxidase can act on histamine itself (Zeller, Stern & Blacksma, 1956), or methylhistamine which is formed in an alternative metabolic pathway of histamine (Schayer & Cooper, 1956). Monoamine oxidase inhibitors affect many other enzymes; those concerned in histamine metabolism include diamine oxidase (Burkard, Gey & Pletscher, 1960; Gey, Pletscher & Burkard, 1963; Shore & Cohn, 1960), and the histamine methylating enzymes (Schayer, 1953; Schayer & Karjala, 1956).

There are species differences in the metabolism of histamine (Schayer, 1956; Tabor, 1956; Zeller, 1956) and these may account for the observed effects of monoamine oxidase inhibitors on responses to histamine in cats and guinea-pigs. That the effects of histamine on blood pressure were enhanced in the cat but not in the guinea-pig, whereas bronchoconstrictor responses were enhanced in the guinea-pig but not in the cat demands a more sophisticated explanation. Possibly, there is a difference in tissue distribution of histamine-metabolizing enzymes in the two species; we have no information about this. Another explanation might be found in the relative sensitivity of the two effector symptoms in the two species. In the cat, histamine is much the more active on the blood pressure, whereas in the guinea-pig it is the more active on bronchial smooth muscle; McCulloch & others (1967) also observed this. Monoamine oxidase inhibitors potentiated the more active component of histamine action in each species. The lack of potentiation of the less active component may be because secondary counteracting mechanisms are enhanced. Thus, in the cat, histamine releases adrenaline as well as having a depressor action, and this is sometimes manifested as a secondary pressor effect, which is enhanced by monoamine oxidase inhibitors. It could also result in bronchodilatation counteracting the bronchoconstrictor action of histamine; Fig. 6 shows such a reduction in bronchospasm together with a marked increase in the secondary pressor response to histamine. The failure of monoamine oxidase inhibitors to enhance the depressor action of histamine in the guinea-pig may be because the dose-response relation for this effect is shallow, as has alo been noticed by our colleagues L. Q. Pun and J. Atkinson (unpublished observations).

Impairment of histamine metabolism by monoamine oxidase inhibitors may allow the accumulation of histamine in the tissues from endogenous sources or from the intake in the diet. The presence of histamine in foodstuffs, along with other amines, has been demonstrated by Blackwell & others (1965) and by Marks (1965). This exogenous histamine is normally metabolized by enzymes present in the gastrointestinal mucosa and thereby detoxified. But, after monoamine oxidase inhibitors, histamine may be absorbed from the intestine and not detoxified. Blackwell & others (1965) found that yeast extracts, including Marmite, contained histamine as well as tyramine. The pharmacological effects of this histamine were greatly enhanced after intraduodenal administration of yeast extract in a cat pretreated with the monoamine oxidase inhibitor mebanazine.

There is no clear evidence that any of the unwanted symptoms occurring with monoamine oxidase inhibitors are due to an increased sensitivity to histamine. Thus, Blackwell & others (1965) noted that asthma, hay fever, allergies and peptic ulcer were not aggravated by monoamine oxidase inhibitors in psychiatric patients. The incidence of headache was high, but it was not effected by dietary items. However,

it is conceivable that potentiation of the action of endogenous histamine may be concerned in the aetiology of these headaches.

Another possible side-effect of monoamine oxidase inhibitors in which histamine may be implicated is hypotension and hypotensive collapse. This has generally attributed to impairment of sympathetic vasoconstrictor tone, but it could be due to histamine-induced vasodilation.

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