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HISTAMINE RECEPTORS IN PERIPHERAL VASCULAR BEDS IN THE CAT

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1 The vasodilator activity of histamine has been studied in anaesthetized cats.

2 Histamine causes dose-dependent vasodilatation in the vasculature of the hind-limb and mesentery, perfused with blood at constant flow.

3 Experiments using the selective antagonists mepyramine and metiamide indicate the involvement of both H_1- and H_2-receptors in the vasodilator responses to histamine. Mepyramine (2.5×10^{-6} mol/kg), causes displacement of the histamine dose-response curve. This displacement is maximum with a dose-ratio of about 10. Further dose-dependent displacement of the dose-response curve occurred after metiamide (4×10^{-7} mol kg^{-1} min^{-1} and 2×10^{-6} mol kg^{-1} min^{-1}), although these does of metiamide had no effect on histamine responses in the absence of mepyramine.

4 Vasodilator responses could also be elicited by the selective H_1-receptor agonists, 2-methylhistamine, 2-(2-aminoethyl)pyridine and 2-(2-aminoethyl)thiazole and the selective H_2-receptor agonist, 4-methylhistamine.

5 The selectivity of mepyramine and metiamide as histamine receptor antagonists was confirmed by their failure to reduce the vasodilator responses to acetylcholine, isoprenaline and bradykinin.

Introduction

In 1910 Dale & Laidlaw observed that in cats, intravenous injections of histamine produced dose-dependent falls in blood pressure due largely to dilatation of resistance vessels. The fall in blood pressure and vasodilatation are only partially blocked by H_1-receptor antagonists (Folkow, Haeger & Kahlson, 1948). It has now been shown that depressor responses to histamine involve both H_1- and H_2-receptors and can only be completely blocked by administration of both H_1- and H_2-receptor antagonists (Black, Duncan, Durant, Ganellin & Parsons, 1972; Owen & Parsons, 1974; Black, Owen & Parsons, 1975).

The present experiments were done to analyse the receptors involved in the vasodilator response to histamine in two major peripheral vascular beds of the cat. Part of this work was presented to the summer meeting of the British Pharmacological Society in Edinburgh, July 1974 (Flynn & Owen, 1974).

Methods

Cats of either sex, weighing between 1.5 and 2.8 kg were anaesthetized by intraperitoneal injection of sodium pentobarbitone (60 mg/kg). Supplementary injections of sodium pentobarbitone were given intravenously if necessary. The trachea was cannulated. The right brachial vein was cannulated for administration of mepyramine or metiamide.

Hind-limb perfusion

Systemic blood pressure was measured from a cannula in the right common carotid artery connected to a Statham P23A blood pressure transducer and recorded on a Devices M8 electronic recorder. The heart rate was measured from the blood pressure pulse using a ratemeter. The left hind-limb was acutely denervated by severing the sciatic nerve bundle in the popliteal cavity. The cat was given heparin 1000 i.u./kg. The right femoral artery was cannulated and blood pumped through silicone rubber tubing by a Watson-Marlow flow inducer at constant pulsatile flow into the left femoral artery. A small segment of thick rubber tubing was inserted into the external perfusion circuit before the pump for injection of drugs. The perfusion pressure was measured by a blood pressure transducer from a side arm in the perfusion circuit between the pump and the perfused hind-limb. At the start of the experiment the rate of flow was adjusted so

that the perfusion pressure was approximately equal to systemic blood pressure and was kept constant at this rate for the duration of the experiment.

Superior mesenteric perfusion

Systemic blood pressure was recorded from the right femoral artery. The inferior mesenteric artery was tied off. The superior mesenteric artery was cleared of connective tissue and the sympathetic nerves around it cut. Blood was taken from the right common carotid artery and pumped through the superior mesenteric artery at constant flow. Perfusion pressure was measured between the pump and vascular bed. As in the hind-limb preparation, drugs were injected into the perfusion system just before the pump.

In both vascular beds intra-arterial injections of vasodilators caused dose-dependent decreases in perfusion pressure, indicating decreases in vascular resistance. When responses, expressed as decreases in perfusion pressure in mmHg, were plotted against $\log_{10}$ dose there was an increase in slope of the linear part of repeated dose-response curves during the course of some experiments. This increase in slope was correlated with a slow increase in perfusion pressure that occurred during the course of these experiments. Expressing the vasodilatation as percentage decrease in perfusion pressure permitted better reproducibility of dose-response curves, eliminating much of the increase in slope.

The effects of mepyramine and metiamide on histamine vasodilatation were determined in both vascular beds. Studies with the histamine-like agonists and non-histamine vasodilators were restricted to the hind-limb vasculature.

In each experiment the doses of agonists were given in random order. Analysis of variance was used to estimate the statistical significance of the results, tests being made for linearity, curvature and parallelism of the dose-response curves. Displacements of the dose-response curves caused by the antagonists were estimated by calculating the potency of the agonist in the presence of the antagonist compared with the potency in the untreated animal, using the data from the analysis of variance.

The slope used in estimating displacements of the dose-response curves was the mean slope of the dose-response curves in that group of experiments.

Drugs used

Histamine acid phosphate (B.D.H.), 2-methylhistamine dihydrochloride, a histamine-like agonist selective for H_1-receptors (Black *et al.*, 1972), 4-methylhistamine dihydrochloride, a histamine-like agonist selective for H_2-receptors (Black *et al.*, 1972), 2-(2-aminoethyl)pyridine dihydrochloride and 2-(2-aminoethyl)thiazole dihydrochloride, both histamine-like agonists selective for H_1-receptors (Lee & Jones, 1949; Grossman, Robertson & Rosiere, 1952; Durant, Ganellin & Parsons, to be published), metiamide, mepyramine maleate (May & Baker), acetycholine chloride (B.D.H.), (−)-isoprenaline hydrochloride (Abbott) and synthetic bradykinin (Sandoz).

Solutions of metiamide were prepared by dissolving the base in a small volume of 0.1 N HCl, neutralizing the solution with 0.1 N NaOH and making up to the required volume with 0.9% NaCl solution.

Histamine, 2-methylhistamine, 4-methylhistamine, 2-(2-aminoethyl)pyridine, 2-(2-aminoethyl)thiazole, acetylcholine, isoprenaline and bradykinin were dissolved in 0.9% NaCl solution. These vasodilators were given by intra-arterial injection into the external perfusion circuit before the pump in volumes of 10-20 μl.

Mepyramine was given by slow intravenous injection. Because of its shorter duration of action, metiamide was given continuous intravenous injection at a flow rate of 0.2 ml/minute. Infusions of metiamide were made for 30 min before and continued during the injection of vasodilators.

Results

Hind-limb vascular bed

Intra-arterial injection of histamine over the dose-range 1×10^{-12} to 1×10^{-7} mol/kg caused dose-dependent decreases in perfusion pressure. Doses greater than 1×10^{-8} mol/kg passed into the systemic circulation and lowered blood pressure.

Administration of the histamine H_1-receptor antagonist, mepyramine (2.5×10^{-6} mol/kg), caused a displacement of the histamine dose-response curve to the right with a dose-ratio of 10.10 (8.7 to 11.7, 95% confidence limits, 4 experiments). Additional doses of mepyramine up to a total cumulative dose of 2.5×10^{-5} mol/kg caused no further displacement of the histamine dose-response curve.

Infusions of the histamine H_2-receptor antagonist metiamide, up to doses of 2×10^{-6} mol kg^{-1} min^{-1}, did not significantly alter the histamine dose-response curve.

Administration of both mepyramine and metiamide together caused a large displacement of the histamine dose-response curve. After maximum displacement of the dose-response curve by H_1-receptor blockade, administration of

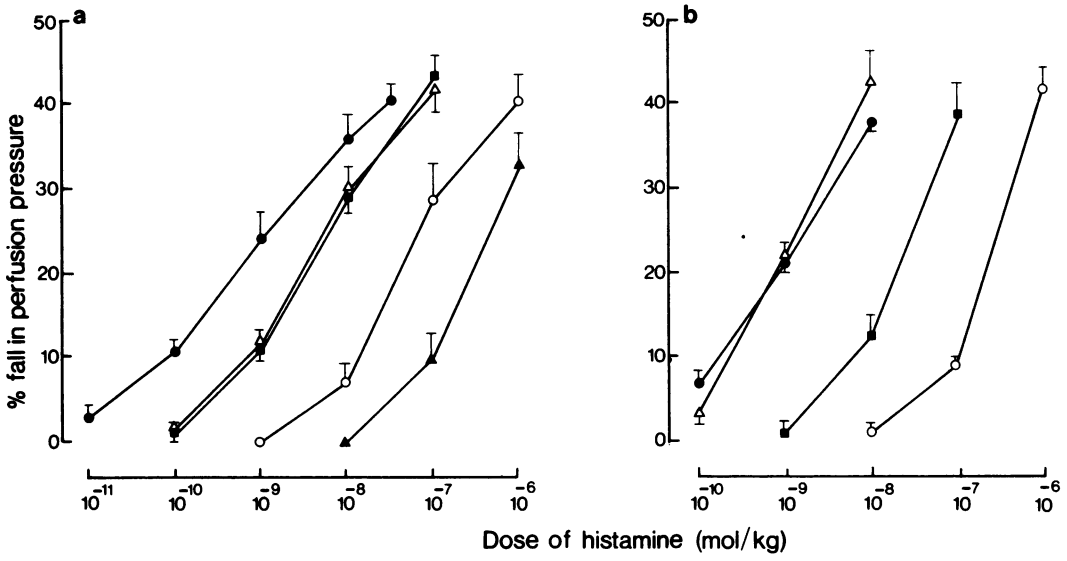

Figure 1 Anaesthetized cats. Vasodilator response to histamine in the hind-limb perfused with blood at constant flow rates. The effects of mepyramine and metiamide on the responses to histamine. (a) Dose-response curve to histamine in untreated cats (•); (△) after mepyramine 2.5×10^{-5} mol/kg; (■) after mepyramine 5×10^{-5} mol/kg; (○) after mepyramine 5×10^{-5} mol/kg plus metiamide 4×10^{-7} mol kg^{-1} min^{-1}; (▲) after mepyramine 5×10^{-5} mol kg^{-1} min^{-1} plus metiamide 2×10^{-6} mol kg^{-1} min^{-1}. (b) Dose-response curve to histamine in untreated cats (•); (△) after metiamide 2×10^{-6} mol kg^{-1} min^{-1}; (■) after metiamide 2×10^{-6} mol kg^{-1} min^{-1} plus mepyramine 2.5×10^{-5} mol/kg; (○) after metiamide 2×10^{-6} mol kg^{-1} min^{-1} plus mepyramine 2.5×10^{-5} mol/kg. Vertical bars indicate s.e. mean.

metiamide caused dose-dependent displacements of the histamine dose-response curve to the right.

Relative to the curve in the presence of mepyramine 5×10^{-5} mol/kg, metiamide caused shifts with dose-ratios of 13.8 (6.9 to 27.8, 95% confidence limits, 4 experiments) at an infusion rate of 4×10^{-7} mol kg^{-1} min^{-1} and 51.6 (22.2 to 119.8, 95% confidence limits, 3 experiments) at an infusion rate of 2×10^{-6} mol kg^{-1} min^{-1}. These changes are illustrated in Figure 1a.

Administration of mepyramine during the infusion of metiamide (2×10^{-6} mol kg^{-1} min^{-1}) caused dose-dependent displacement of the histamine dose-response curve to the right, with dose-ratios of 10.0 (8.4 to 11.8, 95% confidence limits, 6 experiments) and 154 (130 to 183, 95% confidence limits, 6 experiments) at 2.5×10^{-6} mol/kg and 2.5×10^{-5} mol/kg mepyramine respectively. These changes are illustrated in Figure 1b.

Superior mesenteric vascular bed

Intra-arterial injection of histamine over the range 1×10^{-11} to 1×10^{-8} mol/kg caused dose-dependent decreases in perfusion pressure. Doses greater than 1×10^{-8} mol/kg contracted the gut, which interfered with the vasodilatation responses, and some of the histamine passed into the systemic circulation causing depressor responses. The vasodilator responses were linear over the range 1×10^{-11} to 1×10^{-9} mol/kg.

Administration of mepyramine (2.5×10^{-5} mol/kg), caused a displacement of the histamine dose-response curve to the right with a dose-ratio of 16.3 (6.9 to 38.3, 95% confidence limits, 4 experiments). Administration of a further dose of 2.5×10^{-5} mol/kg mepyramine, making a cumulative dose of 5×10^{-5} mol/kg, had no further effect on the dose-response curve. Infusions of metiamide, up to a dose of 2×10^{-6} mol kg^{-1} min^{-1}, had no significant effect on the histamine dose-response curve.

Large displacements of the histamine dose-response curve could be obtained with combinations of the H_1- and H_2-receptor antagonists. Having obtained a maximal displacement of the histamine dose-response curve with mepyramine, 5×10^{-5} mol/kg, the dose-response curve could be displaced further to the right by metiamide 2×10^{-6} mol kg^{-1} min^{-1}, with a dose-ratio of 114 (49 to 264, 95% confidence

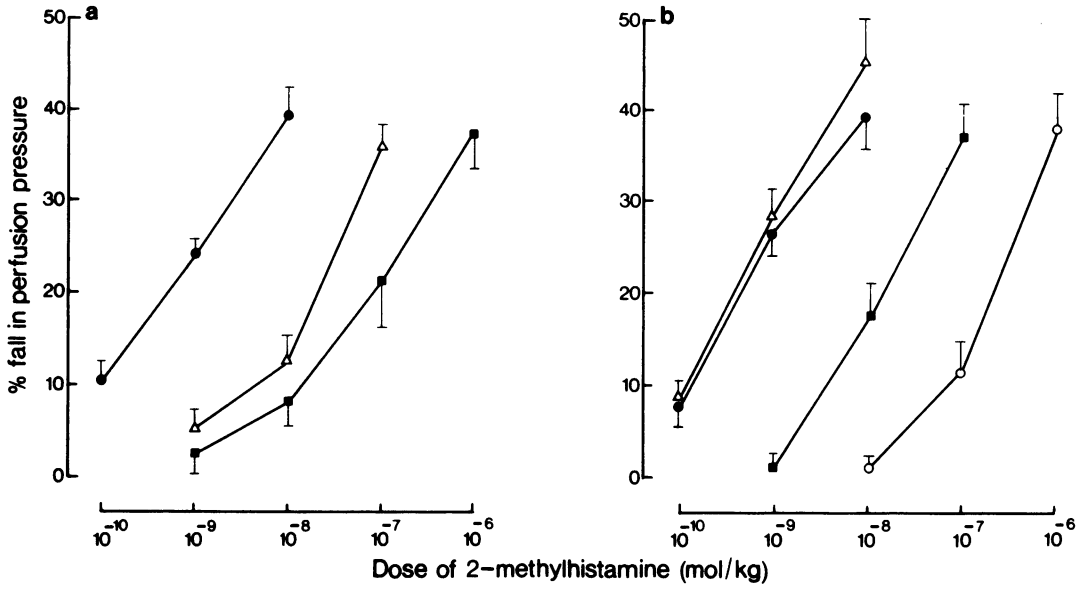

Figure 2 Anaesthetized cats. The effects of mepyramine and metiamide on the vasodilator responses to 2-methylhistamine. (a) Dose-response curve to 2-methylhistamine in untreated cats (•); (△) after mepyramine 2.5×10^{-5} mol/kg; (■) after mepyramine 2.5×10^{-5} mol/kg; plus metiamide 2×10^{-6} mol kg^{-1} min^{-1}. (b) Dose-response curve to 2-methylhistamine in untreated cats (•); (△) after metiamide 2×10^{-6} mol kg^{-1} min^{-1}; (■) after metiamide 2×10^{-6} mol kg^{-1} min^{-1} plus mepyramine 2.5×10^{-6} mol/kg; (○) after metiamide 2×10^{-6} mol kg^{-1} min^{-1} plus mepyramine 2.5×10^{-5} mol/kg. Vertical bars indicate s.e. mean.

limits, 4 experiments) relative to the dose-response curve in the presence of mepyramine.

During infusion of metiamide, 2×10^{-6} mol kg^{-1} min^{-1}, mepyramine caused dose-dependent displacements of the histamine dose-response curve to the right with a dose-ratio of 62.1 (41.5 to 92.7, 95% confidence limits, 4 experiments) at 2.5×10^{-6} mol/kg and a dose ratio of 1,333 (894 to 1989, 95% confidence limits, 4 experiments) at 2.5×10^{-5} mol/kg.

Effect of histamine-like agonists on hind-limb vasculature

2-Methylhistamine caused dose-dependent vasodilator responses over the dose-range 1×10^{-10} to 1×10^{-8} mol/kg. Over this dose-range the dose-response curve was linear. Administration of mepyramine, 2.5×10^{-5} mol/kg, caused a parallel displacement of the 2-methylhistamine dose-response curve to the right (Figure 2a) with a dose-ratio of 29.2 (16.1 to 52.9, 95% confidence limits, 4 experiments), whereas metiamide alone up to 2×10^{-6} mol kg^{-1} min^{-1} had no effect on the 2-methylhistamine dose-response curve. When metiamide (2×10^{-6} mol kg^{-1} min^{-1}) was administered in the presence of mepyramine (2.5×10^{-5} mol/kg) it had no effect on the responses to the smaller dose of 2-methylhistamine, up to 1×10^{-8} mol/kg, but did reduce the responses to larger doses of 2-methylhistamine (Figure 2b).

In the untreated cat, vasodilator responses to 4-methylhistamine were linear over the range 1×10^{-10} to 1×10^{-8} mol/kg. In contrast to the effect of mepyramine on the histamine dose-response curve, administration of mepyramine 2.5×10^{-5} mol/kg, had no effect on the 4-methylhistamine dose-response curve (Figure 3a).

Infusion of metiamide (2×10^{-6} mol kg^{-1} min^{-1}) alone caused a displacement of the 4-methylhistamine dose-response curve to the right (Figure 3b) with a dose-ratio of 11.6 (6.9 to 19.4, 95% confidence limits, 4 experiments). When displaced to the right by metiamide (2×10^{-6} mol kg^{-1} min^{-1}) the 4-methylhistamine dose-response curve was further shifted to the right by administration of mepyramine, 2.5×10^{-6} mol/kg, with a dose-ratio relative to the position of the dose-response curve in the presence of metiamide, of 12.3 (7.3 to 20.6, 95% confidence limits, 4 experiments).

In the untreated cat, responses to

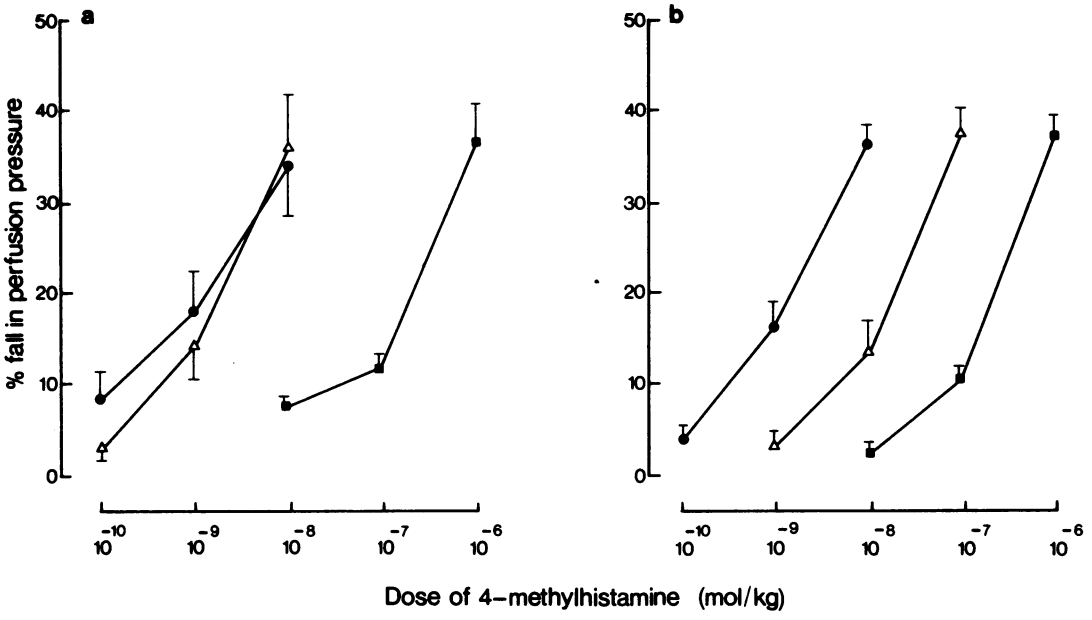

Figure 3 Anaesthetized cat. Effect of mepyramine and metiamide on the vasodilator responses to 4-methylhistamine. (a) Dose-response curve to 4-methylhistamine in untreated cats (●); (△) after mepyramine 2.5×10^{-5} mol/kg; (■) after mepyramine 2.5×10^{-5} mol/kg plus metiamide 2×10^{-6} mol kg^{-1} min^{-1}. (b) Dose-response curve to 4-methylhistamine in untreated cats (●); (△) after metiamide 2×10^{-6} mol kg^{-1} min^{-1}; (■) after metiamide 2×10^{-6} mol kg^{-1} min^{-1}; plus mepyramine 2.5×10^{-6} mol/kg. Vertical bars indicate s.e. mean.

2-(2-aminoethyl)thiazole were linear over the range 1×10^{-10} to 1×10^{-8} mol/kg. Administration of mepyramine caused dose-dependent displacements of the 2-(2-aminoethyl)thiazole dose-response curve to the right, with dose-ratios of 14.3 (10.5 to 19.5, 95% confidence limits) and 44.0 (32.6 to 60.2, 95% confidence limits, 6 experiments), at 2.5×10^{-6} and 2.5×10^{-5} mol/kg respectively. Subsequent administration of metiamide (4×10^{-7} mol kg^{-1} min^{-1}) did not significantly affect the dose-response curve.

In the untreated cat, responses to 2-(2-aminoethyl)pyridine were linear over the range 1×10^{-9} to 1×10^{-7} mol/kg. Administration of mepyramine caused dose-dependent displacements of the 2-(2-aminoethyl)pyridine dose-response curve to the right with dose-ratios of 15.2 (10.5 to 22.0, 95% confidence limits, 6 experiments), and 39.0 (26.6 to 57.1, 95% confidence limits, 6 experiments) at 2.5×10^{-6} and 2.5×10^{-5} mol/kg respectively. Subsequent administration of metiamide (4×10^{-7} mol kg^{-1} min^{-1}) had no effect on the dose-response curve.

Potency of the histamine-like agonists relative to histamine

Each of the agonists was assayed for potency, relative to histamine on vascular H_1- and/or H_2-receptors. The values are shown in Table 1. The assay for H_1-receptor activity was made in the presence of metiamide (2×10^{-6} mol kg^{-1} min^{-1}) to ensure blockade of H_2-receptors; the assay for H_2-receptor activity was made in the presence of mepyramine (2.5×10^{-5} mol/kg) to ensure H_1-receptor blockade.

Specificity of the histamine antagonists

To establish the specificity of mepyramine and metiamide as histamine receptor antagonists, their effects on vasodilator responses to non-histamine-like vasodilators was studied. One dose of bradykinin, acetylcholine, isoprenaline and histamine was determined to give approximately equal sub-maximal responses. The doses used were 3.0×10^{-8} mol/kg acetylcholine, 6.0×10^{-9} mol/kg isoprenaline, 4×10^{-9} mol/kg bradykinin

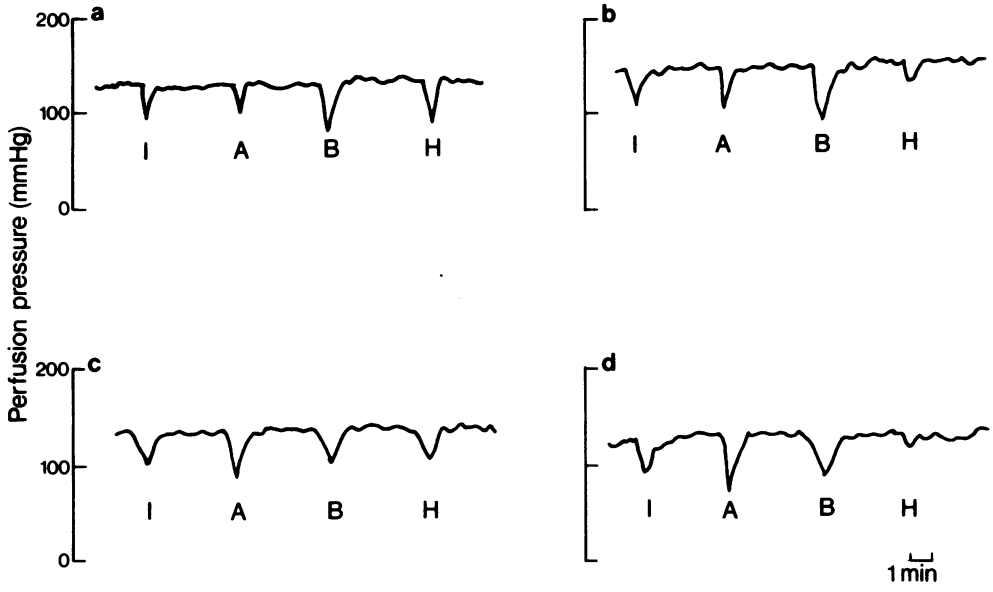

Figure 4 Anaesthetized cats. Effect of mepyramine and metiamide on the vasodilator responses to isoprenaline 6.0×10^{-9} mol/kg at I, acetylcholine 2.8×10^{-8} mol/kg at A, bradykinin 4.0×10^{-9} mol/kg at B and histamine 1×10^{-7} mol/kg at H. (a) Responses in untreated cats. (b) Responses after mepyramine 2.5×10^{-5} mol/kg which reduced the response to histamine but had no effect on the other responses. (c) Responses are shown during infusion of metiamide, 2×10^{-6} mol kg^{-1} min^{-1} which had no effect on the responses. (d) Responses after treatment with mepyramine 2.5×10^{-5} mol/kg plus metiamide 2×10^{-6} mol kg^{-1} min^{-1} which abolished the responses to histamine but had no effect on the other vasodilator responses.

and 1.0×10^{-7} mol/kg histamine. Each dose was given twice and the eight doses given in random order. The eight doses were repeated in the presence of mepyramine (2.5×10^{-5} mol/kg) alone, metiamide (2×10^{-6} mol kg^{-1} min^{-1}) alone and a combination of mepyramine (2.5×10^{-5} mol/kg) and metiamide (2×10^{-6} mol kg^{-1} min^{-1}). The results are shown in Figure 4.

The responses to histamine were reduced by mepyramine alone and by the combination of mepyramine and metiamide. The responses to the other agonists were not significantly reduced by either mepyramine alone, metiamide alone or by the combination of mepyramine and metiamide.

Discussion

The purpose of these experiments was to determine the histamine receptors involved in histamine-induced vasodilatation. Experiments were made in two major peripheral vascular beds and essentially similar results were obtained.

Prior to this, Folkow *et al.* (1948) had shown that whereas the fall in systemic blood pressure and vasodilatation caused by small doses of histamine could be reduced or abolished by H_1-receptor antagonists, the responses to larger doses of histamine were refractory to H_1-receptor antagonists. These findings prompted Folkow *et*

Table 1 Potency of histamine and some histamine-like agonists on vascular H_1- and H_2-receptors

	Potency (95% confidence limits)	
Agonist	*H_1-receptors*	*H_2-receptors*
Histamine	100	100
2-Methylhistamine	15.0 (9.8-23.0)	2.3 (1.4-3.8)
4-Methylhistamine	0.5 (0.3- 0.8)	37.4 (21.4-65.6)
2-(2-Aminoethyl)pyridine	2.3 (1.5- 3.4)	Inactive
2-(2-Aminoethyl)thiazole	13.2 (8.8-17.9)	Inactive

al. (1948) to postulate two types of cardiovascular histamine receptors. This hypothesis of two histamine receptors has subsequently been established and it is now known that the depressor response to histamine involves both H_1- and H_2-receptors (Black *et al.*, 1972; Owen & Parsons, 1974; Black *et al.*, 1975).

The experiments reported in this paper show that both types of histamine receptor are involved in the dilatation of peripheral resistance vessels following local injection of histamine. In untreated animals, the histamine dose-response curves were displaced to the right by mepyramine but unaltered by metiamide, indicating that they were due to interaction of histamine with H_1-receptors and were independent of H_2-receptors. The displacement of the dose-response curve by mepyramine achieved a maximum and then further displacement could only be achieved by H_2-receptor blockade with metiamide, indicating that H_2-receptors were also involved in this response. The inability of metiamide to displace the histamine dose-response curve, although it is able to augment maximal displacement by mepyramine, is consistent with the difference in dissociation constant of the H_1- and H_2-receptors, as referred to in the analysis of the depressor responses to histamine (Black *et al.*, 1975).

Involvement of both H_1- and H_2-receptors in the vasodilator responses to histamine has been established in experiments using selective receptor antagonists. Further support for the involvement of both types of receptor has been obtained using selective receptor agonists. Both 2-(2-aminoethyl)pyridine and 2-(2-aminoethyl)thiazole have been shown previously to be selective H_1-receptor agonists (Lee & Jones, 1949; Grossman *et al.*, 1952; Durant *et al.*, 1974). Both compounds caused dose-dependent depressor responses by interaction with H_1-receptors (Owen, 1975) and have now been shown to cause dose-dependent vasodilatation by interaction with H_1-receptors.

2-Methylhistamine has relatively higher agonist activity on H_1-receptors than on H_2-receptors (Black *et al.*, 1972, Durant *et al.*, 1974; Owen, 1975). 2-Methylhistamine up to doses of about 1×10^{-8} mol/kg given locally caused dose-dependent vasodilatation which was due solely to interaction with H_1-receptors. Doses exceeding 1×10^{-8} mol/kg were no longer specific since interaction with H_2-receptors also occurred.

4-Methylhistamine has relatively higher agonist activity on H_2-receptors than on H_1-receptors (Black *et al.*, 1972; Durant *et al.*, 1974; Owen, 1975). 4-Methylhistamine given locally in doses up to 1×10^{-8} mol/kg caused dose-dependent vasodilatation by interaction with H_2-receptors; larger doses also interacted with H_1-receptors.

Each of the histamine-like agonists mimicked the histamine response. Three of the agonists did so by interaction with H_1-receptors and the fourth, 4-methylhistamine, did so by interaction with H_2-receptors. The experiments with the selective agonists therefore support the conclusion that interaction with either H_1- or H_2-receptors can result in vasodilatation.

The potency of the selective agonists relative to histamine was assayed on both H_1- and H_2-receptors in the peripheral vasculature. The values for both 2-methylhistamine and 4-methylhistamine are similar to the values reported by Black *et al.* (1972) on non-vascular histamine receptors. The values for 2-(2-aminoethyl)pyridine and 2-(2-aminoethyl)thiazole on H_1-receptors are similar to the values found by Owen (1975) on cat blood pressure.

The final part of this study indicated that the effects of mepyramine and metiamide on responses to histamine and histamine-like agonists were the consequence of blockade of histamine receptors rather than non-selective effects as neither antagonist alone nor in combination reduced the responses to three non-histamine-like vasodilators, acetycholine, bradykinin and isoprenaline.

In conclusion, histamine-induced vasodilatation in two major peripheral vascular beds has been shown to involve both H_1- and H_2-receptors. Histamine-like responses can be obtained using selective H_1- or H_2-receptor agonists.

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