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HISTAMINE H_2-RECEPTORS IN THE HUMAN PERIPHERAL CIRCULATION

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Histamine (10 μg/min for 3 min) infused into the brachial artery caused an increase in forearm blood flow which was reduced by mepyramine (25 mg). This effect was most marked in the first minute of the infusion. Metiamide (25 mg) had no effect on the dilatation during the infusion but caused a quicker return of flow to the resting level. The response was abolished when both drugs were given in combination. It is concluded that the response is initiated mainly by stimulation of H_1-receptors and maintained by H_1- and H_2-receptors; continued activity of H_2-receptors may account for the slow return of flow to the pre-infusional level.

Introduction Responses to histamine are mediated by mepyramine-sensitive H_1-receptors or burimamide- and metiamide-sensitive H_2-receptors (Black, Duncan, Durant, Ganellin & Parsons, 1972). Both types of receptor are involved in cardiovascular responses to histamine.

In the rabbit, the change in arterial pressure produced by an intravenous injection of histamine represents a balance between H_1-mediated pressor and H_2-mediated depressor components (Parsons & Owen, 1973; Carroll, Glover & Latt, 1974), and both H_1-vasoconstrictor and H_2-vasodilator receptors have been demonstrated in the same isolated artery (Parsons & Owen, 1973; Glover, Carroll & Latt, 1973). In contrast, both H_1- and H_2-receptors are involved in the vasodepressor response to histamine in the dog and cat. In these species, the response to histamine is partly reduced by mepyramine, and while it is unaffected by burimamide alone, it is abolished when both drugs are given in combination (Black *et al.*, 1972; Parsons & Owen, 1973; Powell & Brody, 1973).

Stimulation of H_1-receptors causes vasodilatation in man, since intra-arterial histamine produces an increase in forearm blood flow which is antagonized by mepyramine (Duff & Whelan, 1954). The role of H_2-receptors has not yet been established, although their activity has been demonstrated in isolated temporal arteries (Glover *et al.*, 1973), and the facial flushing observed during an intravenous infusion of histamine is blocked only when both mepyramine and burimamide are given (Wyllie, Hesselbo & Black, 1972). We now present evidence that both H_1- and H_2-receptors mediate the vasodilator response to histamine in the human forearm.

Methods Blood flow through the forearm was measured in 10 healthy student volunteers by venous occlusion plethysmography (Greenfield, 1954). Isotonic saline (0.9% w/v NaCl solution) was infused at a rate of 4 ml/min through a catheter in the brachial artery; drugs were added to the saline so that the dose for 1 min was contained in 4 ml. Two control infusions of histamine (10 μg/min for 3 min) were given at 10–15 min intervals. The infusions of histamine were repeated twice during the continuous infusion of either mepyramine maleate (5 experiments) or metiamide (5 experiments). The second antagonist was then added to the constant perfusion of saline and two final three min infusions of histamine were given, one at the rate of 10 μg/min and the other 20 μg/minute. The drugs used were histamine acid phosphate (D.G. Bull Laboratory), metiamide (Smith Kline & French) and mepyramine maleate (May & Baker).

Results The results are summarized in Figure 1. Before the administration of an antagonist, histamine caused an immediate and sustained increase in flow followed by a slow return towards the resting level when the infusion ended.

In 5 experiments (Figure 1a) mepyramine 25 mg was infused over 5 min and then given continuously at the rate of 0.25 mg/minute. The response to histamine was reduced but not abolished after 25 mg of mepyramine, and was not reduced further after another 12–15 min of infusion at 0.25 mg/min (3–5 mg of mepyramine). In particular, mepyramine altered the time course of the response. The onset of the vasodilatation was delayed by about 20 s and the average increase during the first minute was 25% of the control response, although it reached a plateau of 49% of the control response during the third minute.

In the other 5 experiments (Figure 1b) metiamide (1 mg/min) was infused continuously and the response to histamine tested after 10 and 25 minutes. Metiamide alone had no effect on the vasodilatation during the histamine infusion, but had a significant effect on the post-infusional dilatation; in the presence of metiamide flow returned to the pre-infusional level in the second minute after the infusion whereas in the third minute after the control infusion flow was still 45% above the resting level. This reduction of the post-infusional vasodilata-

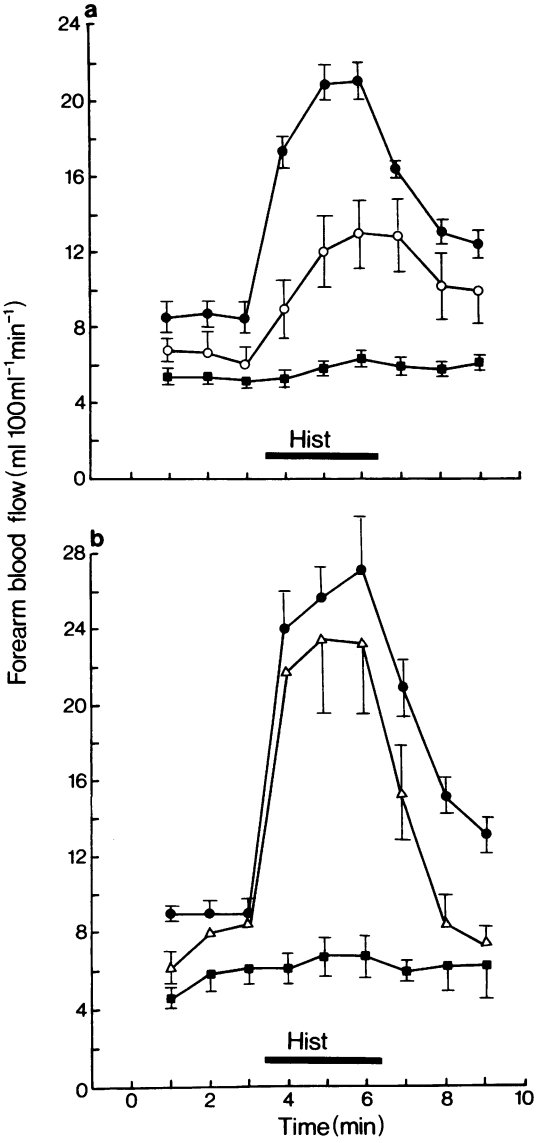

Figure 1 Effect of histamine (10 μg/min for 3 min) on forearm blood flow. Each point is the mean of 3 blood flow rates recorded in each min during 1–2 infusions in each of 5 subjects. Vertical bars show s.e. mean. (●) Control response (2 infusions in each subject); (a) in presence of mepyramine (○) (average of response to 2 infusions, the first after 25 mg, the second after a further 3–5 mg of mepyramine); (b) in presence of metiamide (△) (average of response to 2 infusions, the first after 10 mg, the second after a further 15 mg of metiamide); (■) in presence of both drugs in combination ((a) after mepyramine 30–35 mg and metiamide 10–15 mg; (b) after metiamide 30–40 mg and mepyramine 25 mg).

tion was seen after 10 mg of metiamide, and the response was not altered further after another 15 mg of metiamide.

In all 10 experiments the responses to histamine (10 μg/min for 3 min) and to a further infusion of 20 μg/min for 3 min, were completely abolished when both drugs were given in combination.

Discussion The results show that the vasodilator response to histamine in the human forearm which is only partially attenuated by a large dose of mepyramine is completely abolished when both mepyramine and metiamide are given in combination. It is therefore concluded that the response is mediated by both H_1- and H_2-receptors.

While mepyramine caused a significant reduction in all phases of the response to an infusion of histamine, its effect was most marked in the first minute. Metiamide alone had no effect on the vasodilatation during the infusion but in its presence flow returned more quickly than usual to the pre-infusional level. This suggests that there may be a difference in the time-course of the contributions made by the two types of receptor. The vasodilatation appears to be initiated mainly by stimulation of H_1-receptors and maintained by both H_1- and H_2-receptors. A more prolonged response to stimulation of H_2-receptors may account for the slow return to the pre-infusional level.

Although histamine release has been demonstrated following arterial occlusion and muscular exercise (Anrep, Barsoum, Salama & Souidan, 1944), it has been concluded that histamine does not play a significant role in reactive or post-exercise hyperaemia, since these responses are unaffected or only slightly reduced by antihistamines such as mepyramine (Duff, Patterson & Whelan, 1955). With our present knowledge, this conclusion can only be applied to histamine H_1-receptors and we are now investigating the possibility that H_2-receptors may make a contribution.

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