Time dependence of the interaction between histamine and histamine receptor antagonists in the cardiovascular system

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Depressor and vasodilator responses to injections of histamine in cats and dogs have been shown to involve both H_1- and H_2-receptors (Black, Duncan, Durant, Ganellin & Parsons, 1972; Black, Owen & Parsons, 1975). In contrast, sustained vasodilator responses to histamine are unaffected by H_1-receptors blockade but prevented by H_2-receptor blockade (Grennan, Rooney, Gilbertson & Carson Dick, 1974; Pawlik, Tague, Tepperman, Miller & Jacobson, 1977).

Experiments have been made in sodium pentobarbitone anaesthetized cats (50 mg/kg i.p.), body weight 2.0–3.5 kg. Blood pressure (BP) and heart rate were recorded and aortic blood flow (ABF) measured using an electromagnetic flow probe. Cats were maintained on artificial respiration. Histamine, 2-pyridylethylamine, a selective histamine H_1-receptor agonist (Durant, Ganellin & Parsons, 1975) and dimaprit, a selective H_2-receptor agonist (Parsons, Owen, Durant & Ganellin, 1977), were given by intravenous infusion, for 5 min with an interval of 10 min between.

Histamine infusions (3.16×10^{-9} to 1×10^{-7} mol kg^{-1} min^{-1}), lowered BP and increased ABF. The depressor response was immediate and a clear peak appeared within 30 seconds. Subsequently BP recovered slightly and stabilized from about 2 min onwards. The increase in ABF was also biphasic. Total peripheral resistance (TPR) fell significantly at all doses; the time-course was as described for BP.

Mepyramine (1.25×10^{-5} mol kg^{-1}) and cimetidine (2×10^{-6} mol kg^{-1} min^{-1}) each alone or in combination had no effect on any parameter but each changed the character of the response to histamine. The antagonist combination abolished responses to histamine.

Pretreatment with mepyramine (20 min) antagonised the initial peak depressor response to histamine, dose-ratio 15.63 (9.8–27.03, 95% confidence limits), but had little effect on the sustained response, dose-ratio at 5 min 2.47 (1.53–3.83). Mepyramine almost abolished the initial fall in TPR, displacing the dose-response curve with loss of parallelism; at 5 min the dose-ratio was 3.92 (2.6–5.49). The initial increase in ABF was attenuated by mepyramine and ABF rose slowly during histamine infusion.

Cimetidine pretreatment (20 min) had no effect on the initial depressor response to histamine, dose-ratio 1.26 (0.98–1.68), but reduced the sustained response, dose-ratio at 5 min 3.6 (2.21–5.92). After cimetidine the dose-response curve for the fall in TPR was displaced initially with a dose-ratio of 1.18 (0.96–1.45) and at 5 min with a dose-ratio of 7.69 (4.08–21.28). Cimetidine failed to modify the changes in ABF produced by histamine.

2-Pyridylethylamine (3.16×10^{-8}–3.16×10^{-6} mol kg^{-1} min^{-1}) produced initial falls in BP and TPR; neither of these responses was well sustained. Dimaprit, 1.58×10^{-8}–5×10^{-7} mol kg^{-1} min^{-1}, caused a slower gradual fall in BP and TPR, with peak responses occurring about 3 min into the infusion. Both agonists increased aortic blood flow.

These studies confirm the involvement of both H_1- and H_2-receptors in vasodilator and depressor responses to histamine and provide evidence that the role of each receptor in these responses varies with time. The initial response during infusion of histamine is modified by antagonists as has been described for injections (Owen, 1977), which appear to represent experimental circumstances optimal to demonstrate H_1-receptor involvement. Conversely, sustained responses to histamine involve H_2-receptors and represent circumstances optimal to demonstrate H_2-receptor mechanisms.

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