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DIFFERENTIATION OF THE ROLES OF HISTAMINE H_1- AND H_2-RECEPTORS IN THE MEDIATION OF THE EFFECTS OF HISTAMINE IN THE ISOLATED WORKING HEART OF THE GUINEA-PIG

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1 Differentiation of the roles of histamine H_1- and H_2-receptors in the mediation of the effects of histamine on the isolated working heart of the guinea-pig was achieved through the use of histamine and selective histamine receptor agonists and antagonists.

2 Histamine over the dose range 10^{-9} mol to 10^{-6} mol produced dose-related increases in sinus rate, left intraventricular pressure $(LVP)_{max}$, $LVdP/dt_{max}$, coronary flow, aortic flow, total cardiac output and external pressure-volume work.

3 Dimaprit, a selective histamine H_2-receptor agonist, produced very similar responses to histamine.

4 2-Pyridylethylamine, a selective histamine H_1-receptor agonist, had little effect on cardiac function unless large doses were administered. Such doses produced increases in all measured parameters.

5 Cimetidine, a selective histamine H_2-receptor antagonist, antagonized the effects of histamine and dimaprit and some but not all effects of 2-pyridylethylamine. In the presence of cimetidine a decrease in all parameters with the exception of sinus rate was observed with both histamine and 2-pyridylethylamine.

6 The selective histamine H_1-receptor antagonist, mepyramine, had little effect on responses to all three agonists. However, the depressant effects observed with histamine and 2-pyridylethylamine in the presence of cimetidine were antagonized by mepyramine.

7 The results indicate the important role of the histamine H_2-receptor in the mediation of the gross cardiac effects of histamine and also indicate that histamine H_1-receptors can mediate cardiac depression.

Introduction

The effect of histamine on the heart *in vivo* is complex and although histamine has been shown to change cardiac function *in vivo* (e.g. Levi Capurro & Lee, 1975; Tucker, Weir, Reeves & Grover, 1975), distinction between the direct cardiac effects of histamine and indirect effects due to factors such as reflex responses to hypotension, release of catecholamines from chromaffin tissue and respiratory changes, has proved difficult. As a consequence most studies on the cardiac effects of histamine have been made *in vitro* with a variety of isolated cardiac preparations usually from the guinea-pig. Preparations used include atrial preparations (e.g. Trendelenburg, 1960; Reinhardt, Wagner & Schumann, 1974), right ventricular muscle preparations (e.g. Perez de Gracia & de Mello, 1974; Verma & McNeill, 1977), or whole, Langendorff perfused hearts (e.g. Bartlet, 1963; Levi, 1972).

We have recently described an isolated guinea-pig heart preparation in which the heart is capable of sustaining external work (Flynn, Gristwood & Owen, 1978). In the production of cardiac output and performance of external work the isolated working guinea-pig heart allows a more complete analysis of drug effects on total cardiac function than do non-working hearts. With this preparation the direct cardiac effects of histamine have been investigated in detail. Further, the availability of selective histamine receptor agonists, dimaprit selective for histamine H_2-receptors (Parsons, Owen, Ganellin & Durant, 1977) and 2-pyridylethylamine selective for histamine H_1-receptors (Durant, Ganellin & Parsons, 1975), and also selective histamine receptor antagonists, cimetidine selective for histamine H_2-receptors (Brimblecombe, Duncan, Durant, Emmett, Ganellin & Parsons, 1975) and mepyramine selective for histamine

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H_1-receptors, has allowed the roles of histamine H_1- and H_2-receptors in the mediation of the cardiac effects of histamine to be investigated in detail.

A preliminary account of this work was presented to the British Pharmacological Society (Flynn, Gristwood & Owen, 1977).

Methods

Preparation

Male Dunkin Hartley guinea-pigs within the weight range of 450 to 600 g were killed 20 min after heparin administration (2,000 u i.p.). The heart was rapidly excised and transferred to a beaker containing ice cold perfusion medium, where the lungs and any remaining pericardial tissue were removed. The heart was then mounted on the working heart apparatus which has been described in detail elsewhere (Flynn *et al.*, 1978). When working, a modified Krebs-Henseleit bicarbonate buffer (composition in mM: NaCl 118, KCl 4.7, $NaHCO_3$ 2.5, $MgSO_4$ $7H_2O$ 1.2, $CaCl_2$ 2.55, KH_2PO_4 1.2, glucose 5.0, Na pyruvate 2.0, Ca edetate 0.5), equilibrated with 5% CO_2 in O_2 at 37.5°C, entered the left atrium at a fixed filling pressure of 10 cm H_2O and cardiac output was ejected by the left ventricle against a fluid column, height 70 cm. The perfusion system was a closed system in that under normal conditions both coronary flow and aortic flow were recirculated.

Measurements

Aortic flow was measured with an S.E. Medic 4 mm i.d. electromagnetic cannulating flow probe situated just above the aortic cannula. The probe was connected to an S.E. Medic flow meter (model SEM 275). Left intraventricular pressure (LVP) was measured by inserting a 23 s.w.g. syringe needle into the left ventricle. The needle was connected via a length of fluid-filled polythene tubing to a Bell and Howell pressure transducer (type 4-422). The frequency-response characteristics of the pressure recording system were estimated by obtaining the undamped natural frequency of the system by the transient response method suggested by Fry (1960) and were found to be flat (±5%) up to 13 Hz. The left ventricular pressure signal was differentiated with a Devices differentiator (model 3640) and dP/dt_{max} used as an index of left ventricular contractility. The pressure signal was also used to trigger an instantaneous ratemeter to obtain sinus rate. All four parameters were recorded by means of a Devices M19 six channel recorder. Coronary flow was collected in an inverted T shaped glass vessel of uniform internal bore. One horizontal limb was connected to a Statham P23BC low pressure transducer and by clamping the outflow from the other limb the increase in hydrostatic pressure with time due to the coronary flow could be measured. The pressure was recorded on a potentiometric flatbed recorder and the flow rate determined from the slope of the recording. Total cardiac output was obtained from the sum of aortic and coronary flow. Coronary flow, aortic flow and total cardiac output were expressed per g dry weight of heart tissue, the hearts being dried in an oven at 84°C for a period of 24 h (average dry weight = 0.29 g, $n = 21$). External pressure-volume work was calculated from the formula external pressure-volume work in kg-m min^{-1} g^{-1} = total cardiac output ml min^{-1} g^{-1} × average systolic pressure mmHg × 1.36 × 10^{-5} (see Flynn *et al.*, 1978).

Experimental procedures

Once set up, preparations were left to stabilize for 15 to 20 min and experiments were routinely completed within a further 60 min.

Effects of histamine and histamine agonists Solutions of drugs were administered by bolus injection, 0.5 ml over 5 s, through an injection port situated just before the left atrium. Immediately after drug administration both aortic flow and coronary flow were rejected from the closed system to prevent drug accumulation. Doses were administered at 5 min intervals and a random scheme for administration was employed. Absolute changes in parameters were measured from control values taken immediately before drug injection. All values given are means ± s.e. mean. Full log dose-response curves for each agonist were obtained in separate preparations. Parallel line assays using paired data were additionally carried out to compare the potencies of 2-pyridylethylamine and dimaprit with histamine. For the assays three suitable doses of each agonist were chosen such that at least 2 doses produced submaximal responses on the linear region of the log dose-response curves for each parameter, as indicated from the full log dose-response curves. The doses were administered in random order.

Effects of histamine receptor antagonists Solutions of antagonists were either added to the perfusion medium before the experiment or infused into the closed perfusion system over a 2 min period. The minimum exposure time to antagonists before agonist administration was 15 min for mepyramine and 10 min for cimetidine. Full log dose-response curves for each agonist were obtained in the presence of mepyramine or cimetidine. In further experiments antagonists were administered sequentially. Parallel line assays using paired data were carried out to obtain dose-ratios for histamine and dimaprit in the presence

of various cimetidine concentrations compared with control. For the assays, 3 suitable doses of agonist were chosen, as before, and administered. Cimetidine was then infused into the perfusion system to achieve a desired concentration and 3 appropriately larger doses of agonist administered. A second, higher concentration of cimetidine was then applied and the procedure repeated. In each experiment control responses and responses in the presence of two doses of cimetidine were obtained.

Statistical comparisons and analyses

Where relevant statistical comparisons were made a paired or unpaired Student's t test was used, as indicated. An analysis of variance was performed on paired data to estimate the potencies of dimaprit and 2-pyridylethylamine compared with histamine. An analysis was performed to obtain dose-ratios for each of the four doses of cimetidine used, against histamine and dimaprit. In order to obtain separate estimates of dose-ratios from each experiment the following method was used. The doses of agonist used in the analysis were shown to give responses on the linear part of the full log dose-response curves and the partial log dose-response curves obtained were shown to be parallel by analysis of variance on the results from each group of experiments. It was therefore possible to fit a straight line to results from each individual experiment using a mean slope for the 3 dose-response lines. From the equation of the log dose-response line ($y = ax + b$) for each pair of histamine doses, b was calculated by substituting known values for log dose (x), response (y) and slope (a) into the equation for each point. Mean values for b were obtained and doses required to produce a given response calculated. The ratio of doses to produce a given control response and the same response in the presence of cimetidine gave dose-ratios (DR).

Drugs

Drugs used were: histamine acid phosphate (BDH), 2-pyridylethylamine dihydrochloride (SK&F), dimaprit dihydrochloride (SK&F), cimetidine (SK&F), mepyramine maleate (May & Baker) and propranolol hydrochloride (ICI). All solutions were freshly prepared in 0.9% w/v NaCl solution (saline). Subsequent dilutions were made with perfusion medium.

Results

Effects of histamine

Histamine between 10^{-9} mol and 10^{-5} mol produced dose-related increases in all measured parameters of cardiac function. The full log dose-response curves for histamine are shown in Figure 1. The threshold dose for effect on all parameters was about 10^{-9} mol.

Effects of dimaprit

Dimaprit over a similar dose-range to histamine also produced dose-related increases in all measured parameters of cardiac function. The responses were very similar to histamine responses and the full log dose-response curves for dimaprit on all parameters lay to the right of, were parallel to and had similar maximum increases to the corresponding histamine curves, as shown in Figure 1. The potency of dimaprit relative to histamine (100%) on all parameters was similar, at between 37% and 77% as shown in Table 1.

Effects of 2-pyridylethylamine

2-Pyridylethylamine had little effect on cardiac function except at relatively high doses (greater than 3.16×10^{-6} mol). Such doses produced dose-related increases in all measured parameters of cardiac function. The full log dose-response curves for each parameter lay far to the right of those for histamine and dimaprit, as shown in Figure 1. The analysis of variance used to estimate potency indicated that the dose-response curves for all 3 agonists were parallel over the dose-ranges used for the assay. The relative potency of 2-pyridylethylamine on all parameters with the exception of coronary flow and sinus rate was about 0.2%, on sinus rate and coronary flow the relative potency was higher, as shown in Table 1.

Effects of antagonists alone

Values for parameters obtained after stabilization in the presence of mepyramine 10^{-7} M ($n = 11$), or cimetidine 3.16×10^{-6} M ($n = 11$), or cimetidine 10^{-5} M ($n = 4$) were compared with values from control hearts ($n = 11$) by Student's t test for unpaired data. For all parameters P was greater than 0.05. In further experiments parameters were measured after infusion of cimetidine at 4×10^{-5} M ($n = 3$) and compared with control pre-infusion values by Student's t test for paired data. For all parameters P was again greater than 0.05. These results showed that neither mepyramine nor cimetidine at concentrations used in this study, had any significant effect on cardiac function.

Effects of histamine in the presence of antagonists

Responses to histamine in the presence of mepyramine 10^{-7} M were unmodified. The full log dose-response curves for all parameters obtained in the

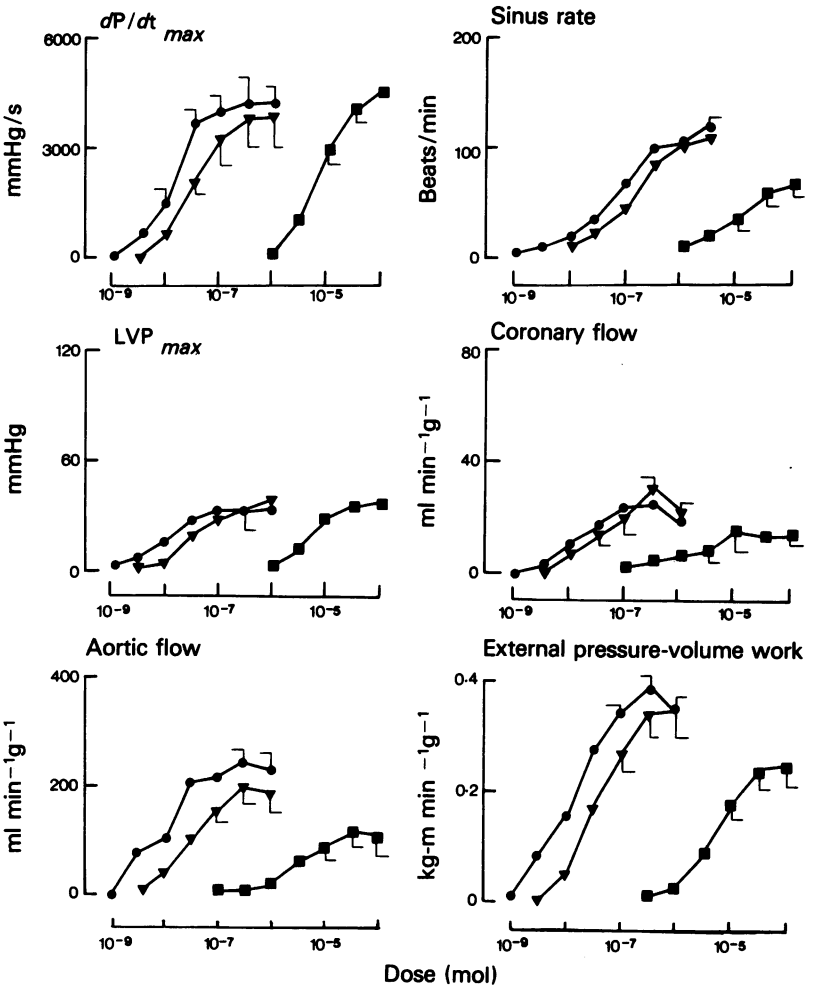

Figure 1 Full log dose-response curves for histamine, dimaprit and 2-pyridylethylamine. Points show the mean absolute increase in each parameter from control values taken immediately before drug injection for histamine (●), dimaprit (▼) and 2-pyridylethylamine (■). For all 3 agonists, $n = 4$. Where large enough, s.e. means are indicated by vertical lines.

Table 1 The potencies of dimaprit and 2-pyridylethylamine relative to histamine (100%) on cardiac function in the isolated working heart of the guinea pig

Parameter	*Dimaprit*	*2-Pyridylethylamine*
Sinus rate	70.9 (50.6 – 99.4)	0.39 (0.30 – 0.50)
LVP_{max}	47.0 (29.3 – 75.5)	0.14 (0.02 – 0.97)
dP/dt_{max}	57.9 (51.3 – 65.4)	0.16 (0.14 – 0.18)
Coronary flow	37.2 (22.1 – 62.4)	0.34 (0.04 – 2.72)
Aortic flow	64.3 (43.1 – 95.9)	0.15 (0.09 – 0.23)
Total cardiac output	76.9 (51.3 – 115.3)	0.23 (0.15 – 0.34)
External pressure-volume work	74.4 (57.2 – 96.8)	0.24 (0.19 – 0.32)

Figures in parentheses indicate fiducial limits. For both agonists $n = 6$.

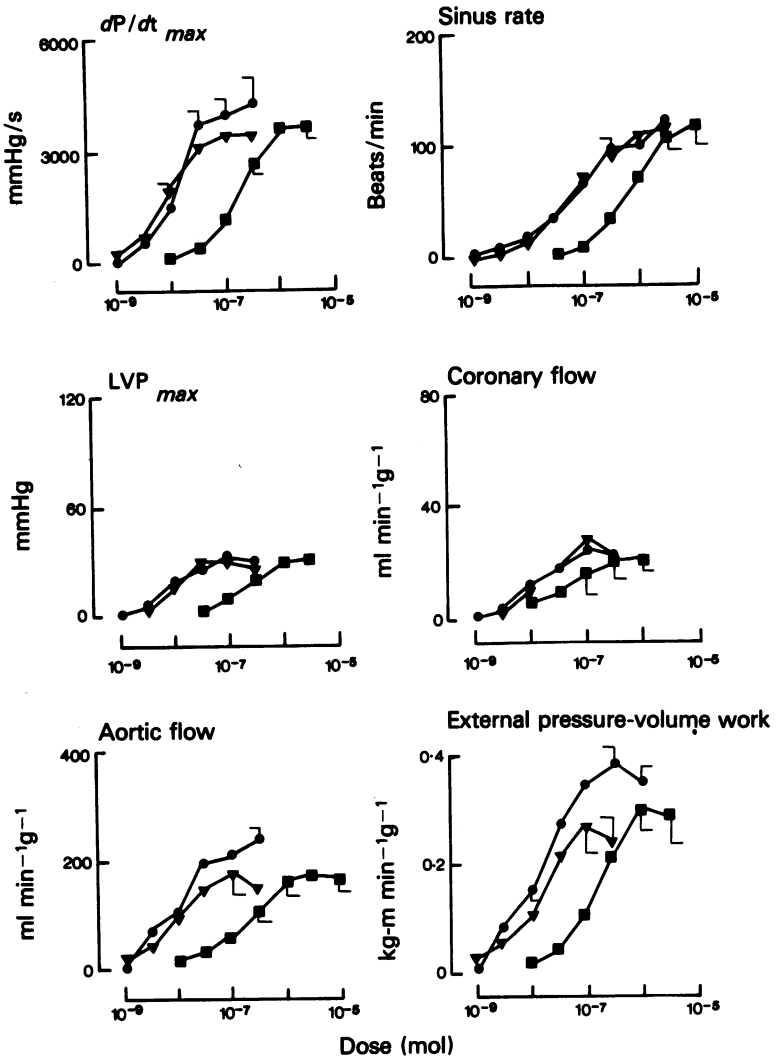

Figure 2 Full log dose-response curves for histamine alone and in the presence of mepyramine 10^{-7} M or cimetidine 3.16×10^{-6} M. Points show the mean absolute increase in each parameter from control values taken immediately before histamine injection, for histamine alone (●, $n = 4$), in the presence of mepyramine (▼, $n = 3$) or cimetidine (■, $n = 4$). Where large enough s.e. means are indicated by vertical lines.

presence of mepyramine were very similar to the control curves as shown in Figure 2.

Cimetidine at 3.16×10^{-6} M antagonized the effects of histamine on all parameters and produced a parallel displacement of the full log dose-response curves to the right with similar maximum increases to control as shown in Figure 2. In contrast to the monophasic coronary flow increases produced by histamine alone, in the presence of cimetidine 3.16×10^{-6} M histamine produced biphasic coronary flow responses consisting of an increase followed by a decrease (2 out of 4 preparations). These effects occurred over a narrow dose range, 10^{-7} mol to 3.16×10^{-7} mol, larger doses producing monophasic increases in coronary flow. In the presence of cimetidine at 10^{-5} M ($n = 4$) and 3.16×10^{-5} M ($n = 3$), histamine over the dose range 10^{-8} to 3.16×10^{-6} mol produced biphasic coronary flow responses consisting of an increase of short duration followed by a more prolonged decrease. In some experiments biphasic changes in coronary flow occurred at doses of histamine which did not produce cardiac stimu-

lation. The decreases in coronary flow were maximal with histamine 3.16×10^{-7} mol in the presence of cimetidine at 10^{-5} M and at 3.16×10^{-5} M, the absolute decreases being -20 ± 2 ml min^{-1} g^{-1} ($n = 4$) and -17 ± 1 ml min^{-1} g^{-1} ($n = 3$) respectively. Over the same dose-range histamine also produced decreases in all other parameters with the exception of sinus rate. Larger doses of histamine tended to produce multiphasic complex responses. The subsequent addition of mepyramine 10^{-7} M abolished the depressant effects of histamine. Where biphasic changes in coronary flow had occurred in the absence of cardiac stimulation, mepyramine abolished both the increase and decrease in coronary flow. In the experiments carried out to obtain dose-ratios for the antagonism of histamine by cimetidine, mepyramine at 10^{-7} M was included in the perfusion medium to antagonize the apparently histamine H_1-receptor mediated depressant effects and the consequential complex responses obtained with larger histamine doses. The analysis of variance performed on the paired data indicated that the mean dose-response curves were parallel. The concentrations of cimetidine used were 10^{-6} M, 3.16×10^{-6} M, 10^{-5} M and 3.16×10^{-5} M. The regression of log (DR-1), obtained by fitting lines to the data as described in the statistical section, on log B (cimetidine concentration), was calculated by a linear least squares fit and 95% confidence limits for the regression obtained. Analysis of variance showed that the sums of squares attributable to a quadratic component in the regression were insignificant. The slopes, with 95% confidence limits for the regression for all parameters were close to unity as shown in Table 2. pA_2 values with 95% confidence limits for cimetidine on all parameters were also calculated from the regression, these were all similar with values between 6.25 and 6.59 as shown also in Table 2.

Effects of dimaprit in the presence of antagonists

Responses to dimaprit in the presence of mepyramine 10^{-7} M were unmodified. The full log dose-response curves for all parameters obtained in the presence of mepyramine were similar to the control curves as shown in Figure 3.

Cimetidine at 3.16×10^{-6} M antagonized the effects of dimaprit on all parameters and produced a parallel displacement of the full log dose-response curves to the right with similar maximum increases to the control curves as shown also in Figure 3. In the experiments carried out to obtain dose-ratios for the antagonism of dimaprit responses by cimetidine, mepyramine 10^{-7} M was included in the perfusion medium. The analysis of variance performed on the paired data indicated that the mean dose-response curves were parallel. Analysis of variance also showed that the sums of squares attributable to a quadratic component in the regression of log (DR-1) on log B was insignificant.

The slopes with 95% confidence limits for the regression on all parameters were close to unity as shown in Table 2. pA_2 values for all parameters were similar and were close to those obtained for histamine (Table 2).

Effects of 2-pyridylethylamine in the presence of antagonists

Responses to 2-pyridylethylamine in the presence

Table 2 pA_2 values and slopes of log (DR-1) versus log antagonist concentration for cimetidine against histamine and dimaprit for all measured parameters of cardiac function

	Histamine		*Dimaprit*	
Parameter	*pA_2*	*Slope*	*pA_2*	*Slope*
Sinus rate	6.59	0.91	6.31	0.94
	(6.30–6.99)	±0.26	(6.08–6.59)	±0.23
LVP_{max}	6.25	1.11	6.45	1.02
	(6.14–6.36)	±0.12	(6.21–6.75)	±0.25
dP/dt_{max}	6.28	1.10	6.44	0.99
	(6.20–6.37)	±0.10	(6.28–6.63)	±0.16
Coronary flow	6.55	1.16	6.50	0.91
	(6.35–6.81)	±0.23	(6.05–7.24)	±0.42
Aortic flow	6.45	1.01	6.33	1.04
	(6.29–6.63)	±0.16	(6.07–6.65)	±0.28
Total cardiac output	6.45	1.05	6.38	1.03
	(6.30–6.62)	±0.15	(6.20–6.59)	±0.19
External pressure-volume work	6.53	1.00	6.49	1.01
	(6.40–6.67)	±0.12	(6.34–6.65)	±0.14

Figures in parentheses indicate 95% confidence limits. In each case $n = 6$.

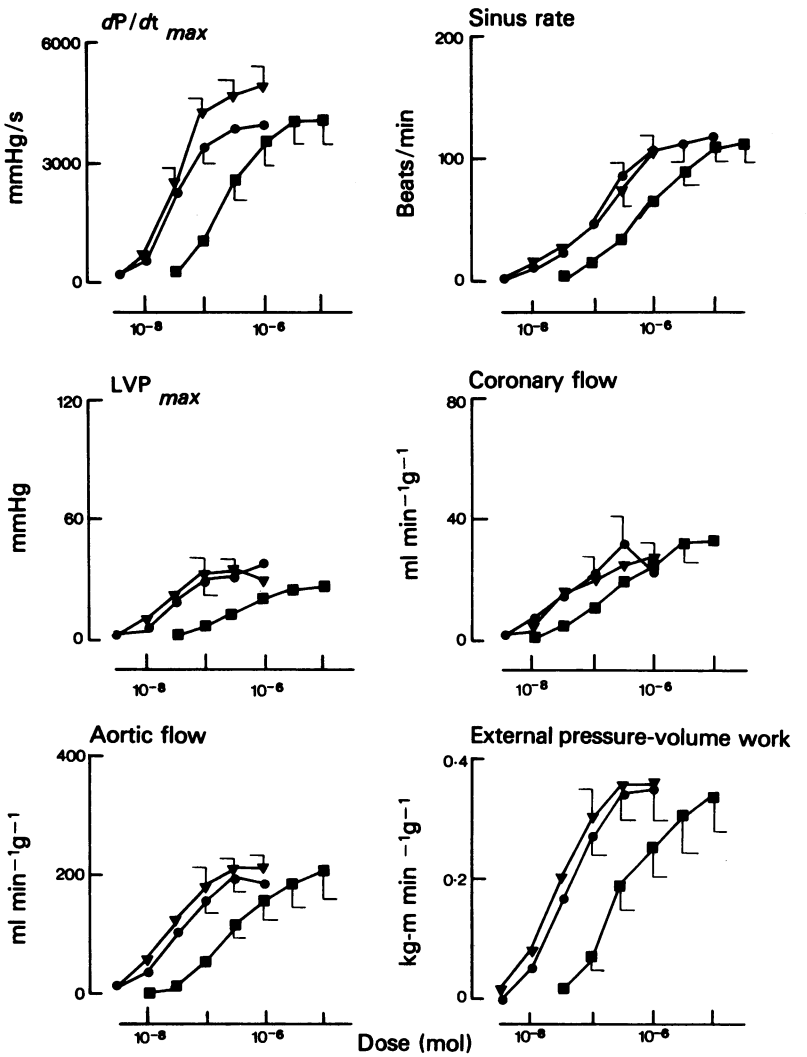

Figure 3 Full log dose-response curves for dimaprit alone and in the presence of mepyramine 10^{-7} M or cimetidine 3.16×10^{-6} M. Points show the mean absolute increase in each parameter from control values taken immediately before dimaprit injection, for dimaprit alone (●, $n = 4$), in the presence of mepyramine (▼, $n = 3$) or cimetidine (■, $n = 4$). Where large enough s.e. means are indicated by vertical lines.

of mepyramine 10^{-7} M were similar to control responses. The full log dose-response curves for all parameters obtained in the presence of mepyramine were essentially similar to the control curves, as shown in Figure 4.

Cimetidine at 3.16×10^{-6} M antagonized the effects of 2-pyridylethylamine on all parameters with the exception of sinus rate and coronary flow (Figure 4). Coronary flow responses were somewhat variable and cimetidine had no obvious effect on these responses. For those parameters which were antagonized, the full log dose-response curves were displaced to the right, the curve for dP/dt_{max} appearing parallel to the control curve. For aortic flow, total cardiac output and external pressure volume work the displacement of curves appeared not to be parallel. In additional experiments the subsequent inclusion of mepyramine 10^{-7} M failed to abolish the cimetidine-resistant heart rate response but the further inclusion of propranolol 10^{-6} M did abolish this response. Where propranolol 10^{-6} M was administered first, a resistant component was identified which was then sensitive to the sub-

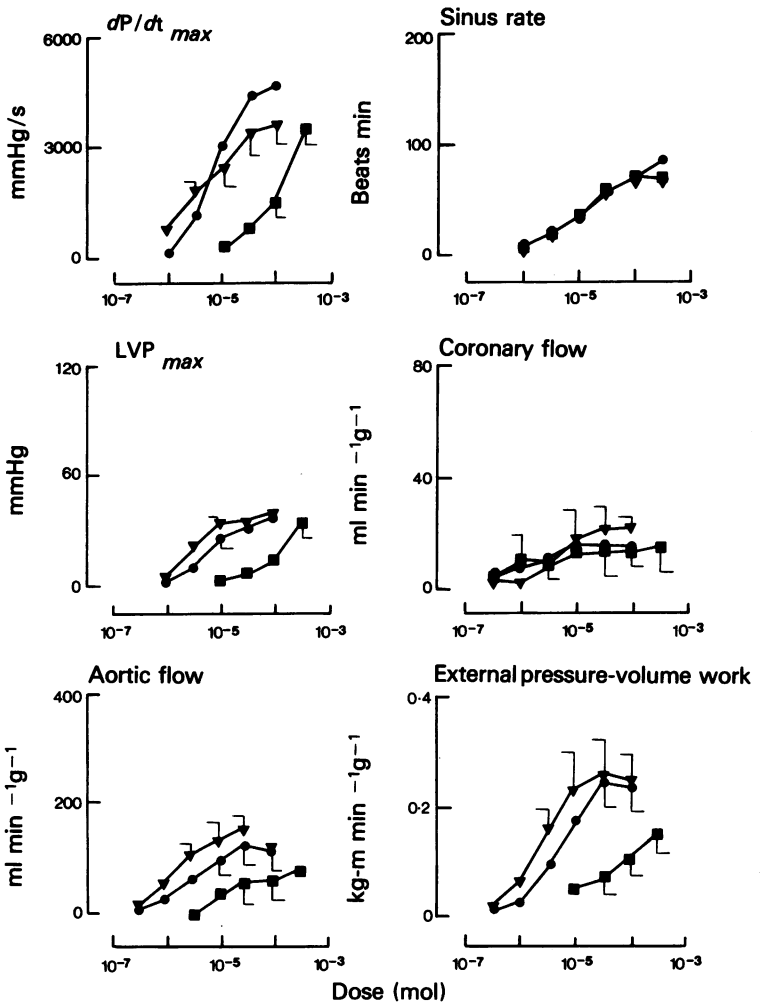

Figure 4 Full log dose-response curves for 2-pyridylethylamine alone and in the presence of mepyramine 10^{-7} M or cimetidine 3.16×10^{-6} M. Points show the mean absolute increase in each parameter from control values taken immediately before 2-pyridylethylamine injection, for 2-pyridylethylamine alone (●, $n = 4$), in the presence of mepyramine (▼, $n = 3$) or cimetidine (■, $n = 4$). Where large enough s.e. means are indicated by vertical lines.

sequent addition of cimetidine. In the presence of cimetidine at 3.16×10^{-6} M in 2 out of 4 preparations doses of 2-pyridylethylamine between 10^{-7} mol and 10^{-6} mol produced biphasic coronary flow responses consisting of an increase of short duration followed by a decrease and also decreases in dP/dt_{max}. In the presence of cimetidine at 3.16×10^{-5} M, 2-pyridylethylamine doses between 10^{-7} mol and 10^{-6} mol) decreased coronary flow and dP/dt_{max} (3 out of 4 preparations). These effects were similar to those seen with histamine in the presence of cimetidine, and were also abolished by the further inclusion of mepyramine 10^{-7} M.

Discussion

In the isolated working guinea-pig heart histamine produced increases in left ventricular contractility as indicated by dP/dt_{max}, sinus rate, LVP_{max}, coronary flow, aortic flow, total cardiac output and external pressure-volume work. The increases in sinus rate, contractility and coronary flow are in agreement with previous studies in which a variety of isolated guinea-pig heart preparations were used. Histamine has been shown to increase the rate of spontaneously beating right atria (e.g. Trendelenburg, 1960; Mannaioni, 1960) and the rate of beating of Langendorff perfused

whole hearts (Bartlet, 1963; Levi, 1972). A histamine-induced increase in the force of contraction of ventricular muscle has been demonstrated in rate controlled (e.g. electrically driven right ventricular strips, Perez de Gracia & de Mello, 1974; Verma & McNeill, 1977) and in spontaneously beating whole Langendorff perfused heart preparations (e.g. Bartlet, 1963; Levi, 1972). In the present study measurement of contractility referred to the left ventricle. It has previously been shown in the isolated working guinea-pig heart under normal conditions that heart rate and contractility are independent (Flynn *et al.*, 1978). This indicates therefore that histamine can cause a direct increase in left ventricular contractility. Histamine has been shown to dilate the coronary vascular bed in Langendorff perfused whole hearts (e.g. Levi, 1972; Broadley, 1975). Broadley (1975), found that the coronary vascular response to histamine was multiphasic although dilatation predominated. In the present study the histamine-induced increases in coronary flow appeared monophasic. In the Langendorff perfused heart a complete analysis of histamine effects on coronary flow has proved difficult as there exists the possibility of both direct and indirect effects, this consideration also applies to the present study. In addition to the effects of histamine on sinus rate, left ventricular contractility and coronary flow, the present study has shown the effects of histamine on LVP_{max}, aortic flow, total cardiac output and external pressure-volume work, all of which were increased.

Dimaprit produced very similar responses to histamine. Dimaprit has been shown to be a full agonist on histamine H_2-receptors with negligible histamine H_1-receptor stimulant activity, having less than 0.0001% the activity of histamine on a histamine H_1-receptor system (Parsons *et al.*, 1977). The relative potency of dimaprit on all measured parameters was between 37% and 77%, values close to the reported value for the relative potency of dimaprit on a cardiac histamine H_2-receptor system, of 71% (Parsons *et al.*, 1977). These results demonstrate therefore that a highly selective histamine H_2-receptor agonist may reproduce very closely the gross cardiac effects of histamine.

The selective histamine H_1-receptor agonist, 2-pyridylethylamine, also increased all measured parameters of cardiac function although these effects occurred with relatively large doses only. The potency of 2-pyridylethylamine relative to histamine on a histamine H_1-receptor system has been reported to be 5.6% (Durant *et al.*, 1975). With the possible exception of effects on coronary flow the relative potency on all parameters was much lower at about 0.2%, with sinus rate a little higher at about 0.3%. The effects of 2-pyridylethylamine on coronary flow were somewhat variable in terms of potency and the 95% confidence limits approached 5.6%, possibly indicating a histamine H_1-receptor-mediated coronary flow increase. Although relatively selective for histamine H_1-receptors, 2-pyridylethylamine possesses demonstrable histamine H_2-receptor stimulant activity with a potency relative to histamine of about 0.2% (Durant *et al.*, 1975). The values obtained for the potency of 2-pyridylethylamine on all parameters with the possible exception of coronary flow and sinus rate were close to this value indicating the possible involvement of histamine H_2-receptors.

Mepyramine had little effect on histamine responses suggesting that histamine H_1-receptors have little role in the mediation of the cardiac effects of histamine. This finding is in agreement with previous studies in the guinea-pig where histamine H_1-receptor antagonists were used. For example, in isolated whole Langendorff perfused hearts, histamine H_1-receptor antagonists have been shown to be unable to antagonize histamine-induced heart rate increases, ventricular contractility and the overall coronary dilatation (Levi & Kuye, 1974; Broadley, 1975). A similar lack of antagonism on contractility has been shown with isolated right ventricular strips (Verma & McNeill, 1977) and on rate (isolated spontaneously beating atria; Trendelenburg, 1960).

Cimetidine antagonized the effects of histamine on all measured parameters. Cimetidine is a competitive histamine H_2-receptor antagonist with a pA_2 value for histamine-induced guinea-pig atrial rate increases of 6.1 (Brimblecombe *et al.*, 1975). In the present study for all measured parameters cimetidine produced a parallel displacement of the full log dose-response curve to the right with similar maximum increases, these being criteria for competitive antagonism. Also the slopes of all regressions of log (DR-1) on log B gave slopes with values close to unity, again indicating competitive antagonism. pA_2 values obtained for all parameters were similar to the reported pA_2 value for cimetidine on guinea-pig atrial rate. These results therefore indicate that the effects of histamine on all parameters in this study were due to an interaction with a single receptor type, namely the histamine H_2-receptor. These results are in agreement with previous studies using histamine H_2-receptor antagonists. The positive chronotropic and inotropic effects and also coronary dilator effects of histamine in guinea-pig whole hearts (e.g. Levi *et al.*, 1975; Broadley, 1975), the positive chronotropic effect in isolated atria (Black, Duncan, Durant, Ganellin & Parsons, 1972; Reinhardt *et al.*, 1974), and the positive inotropic effect in electrically driven right ventricular strips (Verma & McNeil, 1977) are all antagonized by histamine H_2-receptor antagonists.

Histamine produced biphasic coronary flow changes in the presence of cimetidine. All decreases in coronary flow were abolished by mepyramine. The increases in coronary flow which occurred in the

absence of concomitant cardiac stimulation were also abolished by mepyramine. This suggests that histamine H_1-receptors can mediate both coronary vasodilatation and coronary vasoconstriction. These results are in agreement with those obtained by Broadley, (1975) using whole Langendorff perfused hearts, who found that in the presence of the histamine H_2-receptor antagonist burimamide, histamine produced a mepyramine-sensitive biphasic coronary vascular response consisting of a dilatation of short duration followed by a more prolonged constriction. In the present study, histamine in the presence of cimetidine also decreased all other parameters with the exception of sinus rate. These effects were antagonized by mepyramine and would therefore also appear to be the result of histamine H_1-receptor stimulation. Similar although less severe negative inotropic effects were reported by Broadley, (1975), who concluded that this effect was due to coronary vasoconstriction.

Mepyramine had little effect on the responses to dimaprit whereas cimetidine antagonized the effects of dimaprit on all parameters in a competitive manner with pA_2 values similar to those obtained with histamine. These results confirm that the effects of dimaprit on all parameters were due to histamine H_2-receptor stimulation.

Mepyramine did not antagonize the stimulant effects of 2-pyridylethylamine on any parameter, confirming that these effects were not due to histamine H_1-receptor stimulation. Cimetidine antagonized the effects of 2-pyridylethylamine on all parameters with the exception of sinus rate and coronary flow. On left ventricular contractility cimetidine produced a parallel displacement of the full log dose-response curve to the right indicating that this effect was due to histamine H_2-receptor stimulation. This finding in the left ventricle contrasts with results from a previous study by Verma & McNeill, (1977), who reported that the positive inotropic effect of 2-pyridylethylamine on electrically stimulated right ventricle was not antagonized by the histamine H_2-receptor antagonist, burimamide, but was antagonized by promethazine, a histamine H_1-receptor antagonist. Verma & McNeill, (1977) used this evidence to suggest the presence of histamine H_1-receptors in the ventricle. Although these results are at variance with the present findings, the possibility of a difference between left and right ventricle exists. The positive chronotropic effects of 2-pyridyethylamine were not antagonized by cimetidine nor by a combination of cimetidine and mepyramine but were antagonized by the further addition of propranolol indicating a possible β_1-adrenoceptor interaction.

In the presence of cimetidine, 2-pyridylethylamine produced mepyramine-sensitive decreases in coronary flow and contractility. Similar effects were observed with histamine itself in the presence of cimetidine. This further supports the view that histamine H_1-receptors can mediate cardiac depression.

In conclusion, the results indicate the important role of histamine H_2-receptors in the mediation of the cardiac effects of histamine. These receptors mediate increases in sinus rate, the force of contraction of the left ventricle and coronary flow and the interaction of those effects results in the increase of aortic flow, LVP_{max}, total cardiac output and external work. Histamine H_1-receptors appear to play a lesser role in the mediation of cardiac effects. Effects due to histamine H_1-receptor stimulation were not readily observed until the ratio of histamine H_1- to H_2-receptor stimulation was increased through the use of 2-pyridylethylamine or histamine in the presence of cimetidine. These effects included a biphasic effect on coronary flow consisting of an increase of short duration followed by a more prolonged decrease and also the concomitant negative inotropic effects with decreases in aortic flow, LVP_{max} total cardiac output and external work.

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