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The antianaphylactic action of histamine H_2-receptor agonists in the guinea-pig isolated heart

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1 The effects of histamine and of H_1- and H_2-receptor agonists on the response to specific antigen were studied in isolated hearts taken from actively sensitized guinea-pigs.

2 Histamine and H_2-receptor agonists (dimaprit, impromidine) dose-dependently decrease the positive chronotropic and inotropic effects, and the severity of arrhythmias evoked by the challenge of sensitized hearts with specific antigen.

3 Nordimaprit and the selective H_1-receptor agonist 2-pyridyl-ethyl-amine (2-PEA) did not modify the patterns of cardiac anaphylaxis.

4 The positive inotropic and chronotropic responses of the isolated heart to exogenous histamine appear to be partly reduced in the presence of dimaprit.

5 The H_2-receptor agonists decrease the amount of histamine released during cardiac anaphylaxis which is increased by cimetidine, while nordimaprit and PEA were ineffective, indicating an inhibitory function afforded by H_2-receptors in cardiac anaphylaxis.

Introduction

More than 70 years ago Cesaris-Demel described cardiac anaphylaxis as the increase of strength of contraction and the onset of cardiac arrhythmias in isolated heart preparations from sensitized guinea-pigs and rabbits (Cesaris-Demel, 1910). These changes in myocardial function were explained by the release of cardiac histamine as the sole mediator (Giotti *et al.*, 1966), or by the combination of histamine release with the production of vasoactive products of the arachidonic acid cascade (Levi & Burke, 1980).

Apart from any inference concerning the underlying biochemical events, cardiac anaphylaxis is widely recognized as an example of type I hypersensitivity reaction (see Capurro & Levi, 1975, for a review), and the release of cardiac histamine is thought to participate in myocardial damage and arrhythmias (Cameron *et al.*, 1985).

Convincing evidence has been reported that H_2-receptors mediate the inhibition of acute hypersensitivity reactions, both *in vitro* and *in vivo*. *In vitro*, extracellular histamine prevents antigenic release of histamine from cells of allergic donors, the inhibition being reversed by metiamide (Bourne *et al.*, 1971; Lichtenstein & Gillespie, 1973); dimaprit dose-dependently inhibits the immunological histamine release from guinea-pig mast cells, isolated from sensitized animals, in a way which is blocked by cimetidine (Mannaioni & Masini, unpublished observations). *In vivo*, bronchoconstriction induced by antigen in sensitized guinea-pigs is exacerbated by high doses of cimetidine (Dulabh & Vickers, 1978); the H_2-receptor agonist, 4-methyl-histamine, significantly diminished the severity of the anaphylactic reaction in the guinea-pig (Drazen *et al.*, 1978).

While studying the effect of histamine on the release of inflammatory mediators (Fantozzi *et al.*, 1985), we observed that exogenous histamine added to the perfusion fluid bathing guinea-pig isolated hearts taken from sensitized animals, inhibited the positive inotropic and chronotropic and the arrhythmogenic reaction to specific antigen in a concentration-dependent fashion. This observation prompted us to study the effect of H_1- and H_2-receptor agonists on the biochemical and pharmacodynamic responses to specific antigen in the guinea-pig isolated heart.

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Methods

The hearts were isolated from guinea-pigs of either sex (200–400 g) sensitized by two intraperitoneal injections of crystallized ovalbumin (1 ml of 1% solution: Feigen *et al.*, 1960) given on consecutive days. The hearts were taken 15 to 30 days after the sensitization. The isolated organ was perfused with Tyrode solution at 37°C in a modified Langendorff apparatus, at a constant pressure of 40 cm water and gassed with a mixture of 97% O_2, 3% CO_2 giving a final pH of 7.45. The composition of the perfusion fluid was as follows (mM): Na^+ 149.3, K^+ 2.7, Ca^{2+} 1.8, Mg^{2+} 1.05, Cl^- 145.4, HCO_3^- 11.9, $H_2PO_4^-$ 0.4 and (+)-glucose 5.6 (Dieterich & Löffelholz, 1977).

Heart rate and contraction were recorded by means of a pressure transducer connected to a clip on the apex of the heart and recorded on a thermic writing oscillograph. The onset and type of arrhythmias were monitored by means of a bipolar surface electrogram. Coronary perfusates were collected over intervals of 5 min in graduated tubes to determine coronary flow rates. Flow rate through the heart was 3–6 ml min^{-1}.

Cardiac anaphylaxis was elicited by injection into the aortic cannula of 0.1 ml of 1% solution of albumin in Tyrode solution 60 min after the beginning of the perfusion. Perfusates were collected every 5 min for 30 min after the antigen challenge.

The histamine content of the hearts and the perfusates was measured fluorimetrically by the method of Shore *et al.* (1959) as modified by Lorenz *et al.* (1972). The authenticity of the extracted histamine was checked through the fluorescence spectra. In two out of the number of the experiments quoted in brackets, the samples were run in duplicate through the fluorimetric assay and the bioassay on guinea-pig ileum, according to a 2 × 2 design as described by Schild (1942). The two techniques gave similar results. Drugs were added to the perfusion fluid 30 min before the challenge with the antigen and continued until the end of the experiments. At the concentrations present in the perfusates, the drugs did not interfere with the fluorimetric assay of histamine. The values of histamine release were expressed as the percentage of total 'initial' histamine (Mongar & Schild, 1952), i.e. the ratio between histamine appearing in the perfusates and that remaining in the heart. The effect of a given drug on the release of histamine was studied by comparing histamine release in the presence of the drug with a matched control group because of fluctuations in the liberation of cardiac histamine (Giotti *et al.*, 1966).

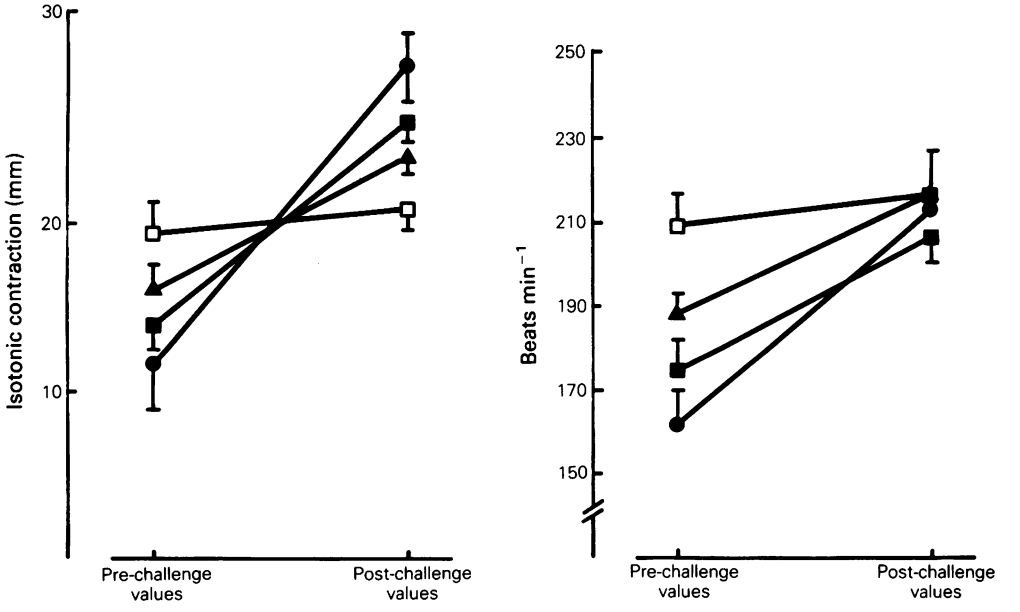

Figure 1 Effect of exogenous histamine on cardiac anaphylaxis *in vitro*. Control (●); histamine 10^{-8} M (■); histamine 10^{-7} M (▲); histamine 10^{-6} M (□). Values are means of 8 experiments with s.e. shown by vertical lines. Measurements were taken at the peak of the anaphylactic response (5 min after antigen injected).

Materials

The chemicals used to prepare the solutions for the fluorimetric assay were of Suprapur quality, E. Merck. *O*-phthaldialdehyde was obtained from B.D.H. Chemicals Ltd. Other drugs used were: histamine dihydrochloride (Calbiochem); egg albumin (Carlo Erba); 2-pyridyl-ethylamine dihydrochloride (2-PEA), dimaprit dihydrochloride, impromidine trihydrochloride, nordimaprit dihydrochloride and cimetidine, were generously supplied by C.R. Ganellin, Smith Kline & French Lab., to whom we are particularly indebted. The drugs were dissolved in Tyrode solution and concentrations are expressed in terms of the base.

Statistical analysis

Student's t test for paired values was used. Differences were regarded as significant if $P < 0.05$. Results are presented as mean ± s.e.mean.

Results

Effects of histamine perfusion on cardiac anaphylaxis

When exogenous histamine was added to the perfusion fluid, the expected increase in both the rate and strength of contraction was observed, depending upon the concentration of histamine (Figure 1). Under these circumstances, challenge of the isolated heart with specific antigen produced an anaphylactic response which was reduced according to the increasing concentrations of exogenous histamine. At a concentration of histamine of 10^{-6} M (the amount of histamine which is actually released during cardiac anaphylaxis: Giotti *et al.*, 1966), the anaphylactic reaction to the specific antigen was virtually abolished.

Effects of histamine H_2-receptor agonists on cardiac anaphylaxis

Antigenic challenge of sensitized hearts resulted in a typical anaphylactic crisis characterized by sinus tachycardia, severe arrhythmias, and an increase in the strength of contraction (Table 1). Perfusion of isolated hearts with dimaprit (10^{-6}–10^{-4} M) produced a slight positive inotropic effect (36.1% at 10^{-4} M, 23.4% at 10^{-5} M, 14.0% at 10^{-6} M). A similar result was obtained with impromidine which increased the strength of contraction by 39.6% at 10^{-5} M and 24.3% at 10^{-7} M.

After measuring the positive inotropic effect, the base-line of the contraction was re-adjusted to values of the same magnitude as the control by varying the transducer amplification, in order to evaluate the post-

Table 1 Effect of histamine H_2-receptor agonists on cardiac anaphylaxis (ovalbumin challenge)

	Concentration of drugs (M)	Contraction (mm)			Heart rate (beats min^{-1})			Incidence of arrhythmias (%)	
		Pre-challenge values	Post-challenge values	% increase	Pre-challenge values	Post-challenge values	% increase	Pre-challenge values	Post-challenge values
Control (7)		14.3 ± 2.1	24.1 ± 4.1	72 ± 3	180 ± 16	220 ± 16	23 ± 6	0	100
Dimaprit (6)	10^{-6}	15.6 ± 3.2	19.3 ± 3.1*	25 ± 7	186 ± 14	213 ± 4*	14 ± 2	0	67.6**
Dimaprit (11)	10^{-5}	14.2 ± 4.2	17.2 ± 2.1*	19 ± 2	198 ± 18	202 ± 8*	3 ± 0.3	0	62.5**
Dimaprit (6)	10^{-4}	13.6 ± 7.2	14.9 ± 1.8*	5 ± 1	228 ± 12	231 ± 4*	0	0	40.0**
Impromidine (4)	10^{-7}	21.6 ± 2.3	28.3 ± 1.0*	35 ± 5	228 ± 4	276 ± 19*	21 ± 4	0	100^{NS}
Impromidine (4)	10^{-5}	22.9 ± 1.7	27.3 ± 3.1*	26 ± 6	251 ± 17	275 ± 15*	6 ± 2	0	75.0**

The number of experiments is given in parentheses.
*$P < 0.001$; **$P < 0.05$; $^{NS}P > 0.05$. P values were obtained by comparing the differences between pre- and post-challenge values within control group and each experimental group (Student's paired t test).
Measurements were taken at the peak of the anaphylactic response (5 min after antigen injection).

Table 2 Effect of 2-pyridyl-ethylamine (2-PEA) on cardiac anaphylaxis (ovalbumin challenge)

	Concentration of drugs (M)	*Contraction* (mm) *Pre-challenge values*	*Post-challenge values*	*% increase*	*Heart rate* (beats min^{-1}) *Pre-challenge values*	*Post-challenge values*	*% increase*	*Incidence of arrhythmias* (%) *Pre-challenge values*	*Post challenge values*
Control (5)	—	15.3 ± 2	23.7 ± 2	60 ± 3	186 ± 8	223 ± 9	31 ± 6	0	100
2-PEA (4)	10^{-7}	16.2 ± 1	24.1 ± 2^{NS}	58 ± 2	169 ± 4	231 ± 6^{NS}	37 ± 2	0	100
2-PEA (4)	10^{-6}	13.1 ± 3	22.3 ± 1^{NS}	59 ± 1	168 ± 7	230 ± 4^{NS}	37 ± 2	0	100
2-PEA (7)	10^{-5}	10.4 ± 2	17.0 ± 2^{NS}	58 ± 2	210 ± 13	285 ± 6^{NS}	36 ± 3	0	100
2-PEA (4)	10^{-4}	13.2 ± 1	19.9 ± 1^{NS}	54 ± 4	198 ± 9	266 ± 4^{NS}	36 ± 4	0	100

The number of experiments is given in parentheses. ^{NS}, $P > 0.05$, see Table 1. Measurements were taken at the peak of the anaphylactic response (5 min after antigen injection).

Table 3 Effect of nordimaprit on cardiac anaphylaxis *(ovalbumin challenge)*

	Concentration of drugs (M)	*Contraction* (mm) *Pre-challenge values*	*Post-challenge values*	*% increase*	*Heart rate* (beats min^{-1}) *Pre-challenge values*	*Post-challenge values*	*% increase*	*Incidence of arrhythmias* (%) *Pre-challenge values*	*Post-challenge values*
Control (4)		15.2 ± 1	25.4 ± 2	68.8 ± 3	178 ± 9	237 ± 8	35.4 ± 1	0	100
Nordimaprit (4)	10^{-6}	17.7 ± 2	28.4 ± 1^{NS}	63.3 ± 4	180 ± 4	244.8 ± 7^{NS}	36.2 ± 2	0	100
Nordimaprit (7)	10^{-5}	16.3 ± 3	25.9 ± 2^{NS}	60.8 ± 1	168 ± 8	225.8 ± 3^{NS}	34.8 ± 1	0	100
Nordimaprit (4)	10^{-4}	15.3 ± 2	19.1 ± 2*	18.3 ± 3	180 ± 7	201.3 ± 2*	12.3 ± 1	0	100

The number of experiments is given in parentheses.
^{NS}, $P > 0.05$, see Table 1. *$P < 0.001$.
Measurements were taken at the peak of the anaphylactic response (5 min after antigen injection).

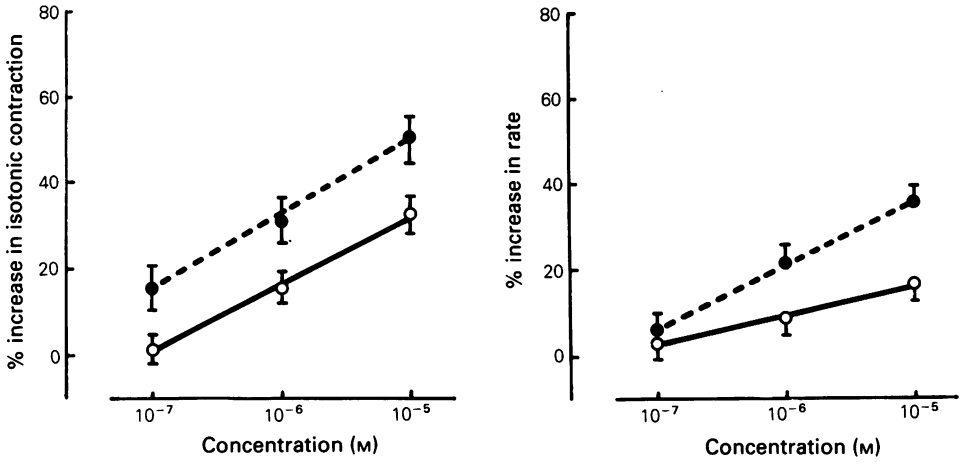

Figure 2 Changes in inotropic and chronotropic responses to histamine in the absence (●) and presence of dimaprit 10^{-6} M (○). Values are means of 5 experiments with s.e. shown by vertical lines. The responses to histamine were evaluated in the same preparations after 30 min of perfusion with dimaprit.

challenge variations. The rate-increasing action of the two agonists is shown in Table 1. In the presence of dimaprit, antigenic challenge of sensitized hearts resulted in a concentration-dependent diminution of the amplitude of the anaphylactic responses (Table 1) which failed to occur at the highest concentrations used. Impromidine was less effective, especially as regards arrhythmias, which were not protected at a concentration of 10^{-7} M.

Effects of nordimaprit and the H_1-receptor agonist 2-pyridyl-ethylamine (2-PEA) on cardiac anaphylaxis

Perfusion of isolated hearts with 2-PEA (10^{-7}–10^{-4} M) failed to alter significantly the strength of contraction; the sinus rate was slightly increased only at high concentrations. In the presence of 2-PEA, at the concentrations given in Table 2, no significant change was observed in the response of the sensitized hearts to challenge with the specific antigen.

Nordimaprit perfusion did not change significantly any cardiac parameters. At the highest concentration (10^{-4} M) nordimaprit inhibited the positive inotropic and chronotropic responses to the antigenic challenge, without influencing the incidence of arrhythmias (Table 3).

Dose-effect responses to exogenous histamine in the absence and in the presence of dimaprit

To check whether the antianaphylactic effect of dimaprit could be due to H_2-receptor occupancy,

Table 4 Anaphylactic release of histamine in perfused guinea-pig heart after treatment with H_2-receptor agonists

	Concentration of drug (M)	*Histamine released* ($\mu g\,g^{-1}$ w.wt) 5′	%	10′	%	15′	%	30′	%	*Residual* ($\mu g\,g^{-1}$ w.wt)	*Total* ($\mu g\,g^{-1}$ w.wt)
Control (8)	—	4.2 ± 1.2	58.1	0.6	8.8	0.2	3.5	0.2	3.3	2.1 ± 0.6	7.4 ± 2.7
Dimaprit (6)	10^{-6}	2.5 ± 1.2*	40.9	0.3*	5.8	0.1*	2.0	0.07*	1.2	3.3 ± 0.9*	6.3 ± 3.8
Dimaprit (8)	10^{-5}	3.2 ± 0.8**	36.6	0.4*	5.9	0.2*	2.4	0.1*	2.0	4.9 ± 1.0**	8.9 ± 2.5
Dimaprit (5)	10^{-4}	1.4 ± 0.3**	19.7	0.1**	2.1	0.09**	1.3	0.08**	1.2	5.6 ± 0.4**	7.3 ± 2.3
Impromidine (3)	10^{-5}	3.8 ± 0.7*	45.3	0.5*	6.9	0.1*	2.1	0.1*	2.1	3.9 ± 1.1*	8.5 ± 3.2
Nordimaprit (8)	10^{-5}	4.2 ± 0.4^{NS}	53.0	0.7^{NS}	8.7	0.2^{NS}	3.2	0.2^{NS}	2.8	2.7 ± 0.9^{NS}	8.1 ± 0.9

The number of experiments is given in parentheses.
*$P < 0.05$, experimental groups versus control; **$P < 0.001$; ^{NS}, $P > 0.05$.

Table 5 Anaphylactic release of histamine in perfused guinea-pig heart after treatment with 2-pyridyl-ethylamine (2-PEA)

	Concentration of drugs (M)	*Histamine released* ($\mu g\,g^{-1}$ w.wt) 5′	%	10′	%	15′	%	30′	%	*Residual* ($\mu g\,g^{-1}$ w.wt)	*Total* ($\mu g\,g^{-1}$ w.wt)
Control (5)	—	2.7 ± 0.9	43.6	0.4	6.6	0.2	3.4	0.1	3.0	2.9 ± 0.9	6.3 ± 2.7
2-PEA (4)	10^{-7}	2.9 ± 0.3^{NS}	39.7	0.4^{NS}	6.2	0.2^{NS}	3.1	0.2^{NS}	2.9	3.7 ± 1.1^{NS}	7.4 ± 2.7
2-PEA (4)	10^{-6}	3.4 ± 0.1^{NS}	39.1	0.5^{NS}	6.7	0.3^{NS}	4.1	0.1^{NS}	1.7	4.4 ± 0.8^{NS}	8.7 ± 0.3
2-PEA (4)	10^{-5}	2.4 ± 0.7^{NS}	36.7	0.4^{NS}	6.1	0.2^{NS}	3.6	0.1^{NS}	2.9	3.6 ± 0.8^{NS}	6.7 ± 1.7

The number of experiments is given in parentheses.
NS, $P > 0.05$, experimental groups versus control.

experiments were carried out to measure the dose-effect responses to exogenous histamine in the absence and presence of dimaprit.

In the absence of dimaprit, histamine increased heart contractility and frequency. After perfusion with dimaprit (10^{-6} M) for 30 min, the final histamine response was significantly depressed when compared to the initial response (Figure 2).

Effect of H_1- and H_2-receptor agonists and cimetidine on the release of histamine in cardiac anaphylaxis

The overall histamine release was evaluated within 30 min after antigenic challenge; in control experiments 39–50% of the endogenous histamine was released, a similar result to that of previous experiments (Giotti *et al.*, 1966). In the presence of dimaprit and impromidine, the amount of histamine released after exposure to specific antigen was significantly decreased (Table 4). No significant variation in the release of histamine was observed in the presence of different concentrations of nordimaprit and 2-PEA (Table 4 and 5). In the presence of cimetidine, 10^{-7} M to 10^{-5} M, the amount of histamine released after exposure to specific antigen was significantly higher than the control values (Table 6), although this was not a dose-dependent effect.

Discussion

The present results indicate that exogenous histamine and two H_2-receptor agonists of unrelated chemical structure caused a concentration-dependent inhibition of the responses of sensitized guinea-pig heart to specific antigen, whilst decreasing the antigenic release of histamine. Histamine and H_2-receptor agonists have been shown to inhibit mediator release *in vitro* by stimulation of H_2-receptors on tissue mast cells or basophils (Lichtenstein & Gillespie, 1973; 1975; Masini *et al.*, 1982a,b) and by increasing cyclic adenosine monophosphate. This finding led to the suggestion that histamine released by an immediate hypersensitivity reaction may participate in feedback inhibition on sensitized cells and act to limit the severity of the reaction. It is therefore possible that stimulation of H_2-receptors would decrease inflammatory reactions in acute allergic challenge: dimaprit has been reported to inhibit histamine release from human basophils (Rising & Lewis, 1982) and from sensitized guinea-pig mast cells exposed *in vitro* to specific antigen (Mannaioni & Masini, unpublished observations).

In isolated cells, it remains unclear whether the H_2-mediated inhibition of histamine release is coupled with the stimulation of adenylate cyclase activity and

Table 6 Anaphylactic release of histamine in perfused guinea-pig heart after treatment with cimetidine

	Concentration of drugs (M)	*Histamine released* ($\mu g\,g^{-1}$ w.wt) 5′	%	10′	%	15′	%	30′	%	*Residual* ($\mu g\,g^{-1}$ w.wt)	*Total* ($\mu g\,g^{-1}$ w.wt)
Control (5)	—	2.6 ± 0.5	36.9	0.5	7.7	0.3	4.2	0.2	3.1	3.7 ± 0.6	7.3 ± 0.6
Cimetidine (6)	10^{-7}	4.3 ± 0.6*	58.3	0.4^{NS}	6.2	0.2^{NS}	4.0	0.2^{NS}	2.9	2.3 ± 0.7*	7.4 ± 1.3
Cimetidine (6)	10^{-6}	4.2 ± 0.2*	49.3	0.6^{NS}	7.9	0.2^{NS}	3.4	0.2^{NS}	2.8	3.5 ± 0.3^{NS}	8.7 ± 0.3
Cimetidine (6)	10^{-5}	4.0 ± 0.3*	61.3	0.5^{NS}	8.0	0.2^{NS}	3.6	0.1^{NS}	1.7	1.9 ± 0.4*	6.7 ± 1.7

The number of experiments is given in parentheses.
*$P < 0.05$, experimental groups versus control.
NS, $P > 0.05$.

the consequent increase in cyclic AMP levels. In the heart, a number of early studies demonstrated that histamine stimulates adenylate cyclase in broken cell preparations of cardiac muscle (Klein & Levey, 1971), by means of an H_2-response, since burimamide caused a parallel shift in the histamine dose-response curve, suggesting a competitive inhibition (Verma & McNeill, 1974).

Dimaprit and impromidine also caused a significant stimulation of basal adenylate cyclase activity of guinea-pig ventricles (Johnson *et al.*, 1979; Johnson, 1982). The affinities of the H_2-receptor agonists for cardiac adenylate cyclase were virtually identical to their affinities for physiological H_2-receptors (Johnson, 1982). On the other hand, the H_1-receptor agonist 2-pyridyl-ethylamine was virtually devoid of any activating properties on cardiac adenylate cyclase and did not produce any significant increase either in heart rate or strength of contraction (Johnson & Mizoguchi, 1977). Thus, the antianaphylactic action of histamine and histamine H_2-receptor agonists could be explained by assuming an H_2-mediated stimulation of cardiac adenylate cyclase leading to increased cyclic AMP levels and the consequent inhibition of immunological histamine release, in keeping with the hypothesis that cyclic AMP inhibits antigen-stimulated histamine secretion by blocking calcium transport across the mast cell membrane (Foreman *et al.*, 1975; 1977; Foreman, 1981). However, the cyclic AMP-mediated inhibition of histamine release has been reported to occur in isolated mast cells, while the H_2-mediated stimulation of cardiac adenylate cyclase refers to an overall situation, including significant cell types other than the mast cells, such as myocytes, nerve terminals, smooth muscle cells and capillary endothelium. Each of these cell types may possess histamine H_2-receptors (the presence of adenylate cyclase has been demonstrated in both the myocyte and the capillary endothelium: Wollenberger *et al.*, 1973) and may contribute to the observed changes in cyclic AMP levels making uncertain the magnitude of the contribution of cardiac mast cells, and rendering critical the correlation between high levels of cardiac cyclic AMP and the inhibition of antigenic histamine release. Furthermore, this correlation is even dubious in isolated mast cells since the study of Fredholm *et al.* (1976), which showed that papaverine and isobutylmethylxanthine both elevate the cyclic AMP levels but only papaverine inhibits histamine release effectively. The antianaphylactic effects of histamine and histamine H_2-receptor agonists could also be explained in terms of unspecific receptor occupancy. In isolated rabbit atria, a control dose of histamine (4.5×10^{-6} M) produced the expected increase in rate. After perfusion with dimaprit (1.4×10^{-4} M for 60 min) there was an 80% reduction in the histamine response, which was still depressed by approximately 25% when compared to the initial response even after the tissues had been washed (Hughes, 1980). Our present results agree with the experiments reported by Hughes and indicate that dimaprit may act as a partial agonist.

In addition, the ineffectiveness of nordimaprit and the H_1-receptor agonist (2-PEA) and the increased release of histamine observed in the presence of cimetidine strengthen the hypothesis that H_2-receptors may be involved in the modulation of cardiac anaphylaxis.

It is therefore possible that the decrease of cardiac anaphylaxis, as observed in the presence of histamine, dimaprit and impromidine, could be produced both by the reduction of histamine release and the H_2-receptor occupancy.

In conclusion, these results point to H_2-receptor agonists as potentially useful drugs in reducing the release of histamine, while increasing the strength of myocardial contractility. These drugs are already in use in clinical trials on patients with catecholamine-refractory heart failure (Baumann *et al.*, 1982). Moreover, one of us has recently demonstrated that dimaprit was able to decrease the number of ventricular arrhythmias in dogs with subacute coronary thrombosis (Masini *et al.*, 1985).

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