Br. J. Pharmac. (1975), 54, 511-521

THE ROLE OF H_1 AND H_2-RECEPTORS IN THE CORONARY VASCULAR RESPONSE TO HISTAMINE OF ISOLATED PERFUSED HEARTS OF GUINEA-PIGS AND RABBITS

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1 The effects of histamine on the isolated perfused hearts of guinea-pigs and rabbits were examined. Records of contractile force, heart rate and coronary perfusion pressure were obtained.

2 Histamine exerted positive inotropic and chronotropic effects which were antagonized by burimamide and attributed to stimulation of H_2-receptors.

3 The coronary vascular response to histamine differed between guinea-pigs and rabbits. In guinea-pig hearts, three phases were apparent: (a) An initial vasodilatation preceding any effects on heart force and rate was antagonized by mepyramine and therefore mediated by histamine H_1-receptors in the coronary circulation. (b) A secondary vasoconstriction was attributed to the increased myocardial compression during the positive inotropic and chronotropic responses. (c) The final, more predominant, component was a prolonged vasodilatation probably associated with the increased metabolic activity of the heart.

4 The latter two components were abolished together with the myocardial responses by burimamide. The remaining coronary vascular response was biphasic, consisting of a vasodilatation immediately followed by vasoconstriction. Both were antagonized by mepyramine and therefore mediated by H_1-receptors.

5 The coronary vascular response of rabbit hearts was similar but no direct vasodilatation was observed and it was concluded that histamine receptors in the coronary vasculature involve only vasoconstriction.

Introduction

The stimulant effects of histamine on the heart have been shown to be antagonized by the classical antihistamines to varying degrees. Complete antagonism of the positive inotropic and chronotropic responses was claimed by Dews & Graham (1946) and Mannaioni (1960), while Bartlet (1963) and Levi & Kuye (1974) failed to show any antagonism. Others (Trendelenburg, 1960; Flacke, Atanacković, Gillis & Alper, 1967; Fantozzi, Ledda, Mannaioni, Moroni & Mugelli, 1974; McNeill & Verma, 1974a) have found only partial inhibition. This has been termed non-specific by Trendelenburg (1960) since concentrations in excess of 10^{-6} M were required, thus yielding a low pA_2 value of 5.3 compared with 9.0 obtained in the guinea-pig intestine. McNeill & Verma (1974a) found that promethazine in concentrations above 8×10^{-6} M depressed the maximum response to histamine and concluded that the antagonism was of a non-competitive nature. Since these concentrations of the antihistamine also tend to depress the rate and force of contractions (Levi & Kuye, 1974) probably by their local anaesthetic action (Trendelenburg, 1960), it is not surprising that the histamine and indeed nicotine (Trendelenburg, 1960) and noradrenaline (McNeill & Verma, 1974a) are also inhibited. The failure of these antihistamines satisfactorily to antagonize the effects of histamine on the heart and several other tissues in concentrations more appropriate to typical antihistamine activity, led to the suggestion that there are two classes of histamine receptors. Those sensitive to classical antihistamines were designated H_1-receptors (Ash & Schild, 1966). This was further substantiated by the introduction of burimamide, a selective antagonist of those effects previously unaffected by antihistamines and therefore mediated by H_2-receptors (Black, Duncan, Durant, Ganellin & Parsons, 1972). Burimamide effectively blocks the positive inotropic and chronotropic responses to histamine

(Black *et al.*, 1972; Capurro & Levi, 1973; Levi & Lee, 1974; McNeill & Verma, 1974b; Levi, Capurro & Lee, 1975).

On the coronary circulation histamine produces vasodilatation revealed as an increased coronary blood flow (Wégria, 1951; Charlier, 1961; Parratt, 1968). This response has been prevented in the guinea-pig perfused heart by the H_2-receptor antagonist metiamide, concomitantly with the antagonism of the tension and rate changes (Ercan, Bökesoy & Türker, 1974). All three responses were unaffected by mepyramine. They therefore concluded that the coronary vasodilatation in response to histamine is mediated via H_2-receptors in the coronary vasculature. However, they did not make allowance for the simultaneous blockade of the myocardial responses which may well have indirectly modified the vascular response. Flacke *et al.* (1967) also reported failure of the classical antihistamines to antagonize the increased coronary blood flow to histamine in dog heart-lung preparations. In contrast, Levi & Kuye (1974), using guinea-pig isolated hearts, have antagonized the histamine-induced increase in coronary flow by five classical H_1-antagonists. They suggest the presence of H_1-receptors in the coronary circulation. These contradictory views pose the question that both H_1- and H_2-receptors may be involved and that these authors are recording different components of the response. The present study was undertaken to examine the coronary vascular response of guinea-pig isolated hearts to histamine in order to determine whether there are several phases and the role of the simultaneous myocardial changes which were ignored by Ercan *et al.* (1974). Then the systematic use of both types of antagonist would attempt to clarify whether H_1- or H_2-receptors or both are involved in the coronary vascular response.

Finally, in view of certain reported species differences to histamine on vascular smooth muscle, an examination has also been made of the effects in rabbit hearts. For example, in the cat, rat and dog, histamine exerts vasodepressor responses through stimulation of both H_1- and H_2-receptors, whereas in the rabbit, rises in blood pressure are mediated through H_1-receptors (mepyramine-sensitive) and falls in pressure through H_2-receptors (burimamide-sensitive) (Parsons & Owen, 1973).

Methods

Guinea-pigs of either sex and weight range 450-650 g were killed by a blow on the head. The hearts were rapidly excised and transferred to a beaker containing Krebs-bicarbonate solution, where associated pericardial tissue and lung tissue were trimmed free. The cut aorta was tied into a glass cannula for retrograde perfusion of the coronary circulation by a modification (Broadley, 1970) of the Langendorff (1895) method.

A constant rate of perfusion (5 or 6 ml/min depending on animal weight) was produced with a Watson-Marlow flow inducer (MHRE/30/T, 0.8 mm tube bore). The Krebs-bicarbonate solution (composition in g/l distilled water: NaCl 6.92, KCl 0.345, $CaCl_2 2H_2O$ 0.28, $NaHCO_3$ 2.1, $MgSO_4 7H_2O$ 0.29, glucose 2.0, $NaH_2PO_4 2H_2O$ 0.16) was gassed with 5% CO_2 in O_2 before entering the flow inducer, it then passed to a warming coil (37.5°C) at the base of which was the aortic cannula. Alterations in perfusion pressure (resting level between 25 and 50 mmHg (1 mmHg ≈ 133 Pa), arising from changes in coronary vascular resistance were recorded on a Devices M19 polygraph by means of a pressure transducer (Consolidated Electrodynamics Type 4-327-L221) situated at a side-arm of the aortic cannula. A Condon manometer was also included in the system at this point to accommodate some degree of volume change during drug responses.

Isometric contractions of the hearts were recorded with a transducer (Ether, Type UF1, 57 g sensitivity range) attached via a pulley to a clip on the apex of the ventricles. The transducer was adjusted so that a diastolic tension of 1-2 g was applied to the hearts. The heart rate was recorded with a ratemeter (Devices, Type 2751) triggered by the signal from the tension record.

Experiments were also performed with hearts from rabbits (Norfolk White strain) of either sex and weight range 1 to 1.5 kg. These were set up identically, except that a perfusion rate of 8 ml/min was required.

Drugs were injected into the perfusion solution through the connecting rubber tubing immediately prior to entry into the warming coil. The dose volume was between 0.025 and 0.2 ml and this produced a small injection artefact which was well separated from the drug response. Antagonists were usually added to a Ringer solution reservoir.

Drugs used were: burimamide (SK & F Labs Ltd.), histamine acid phosphate (Sigma), mepyramine maleate (Anthisan, May & Baker Ltd.). All solutions were freshly prepared in 0.9% w/v NaCl solution (saline) and amounts referred to in the text are expressed as the base.

Results

Figure 1 illustrates a typical response to histamine (1 μg) of the guinea-pig perfused heart. The force

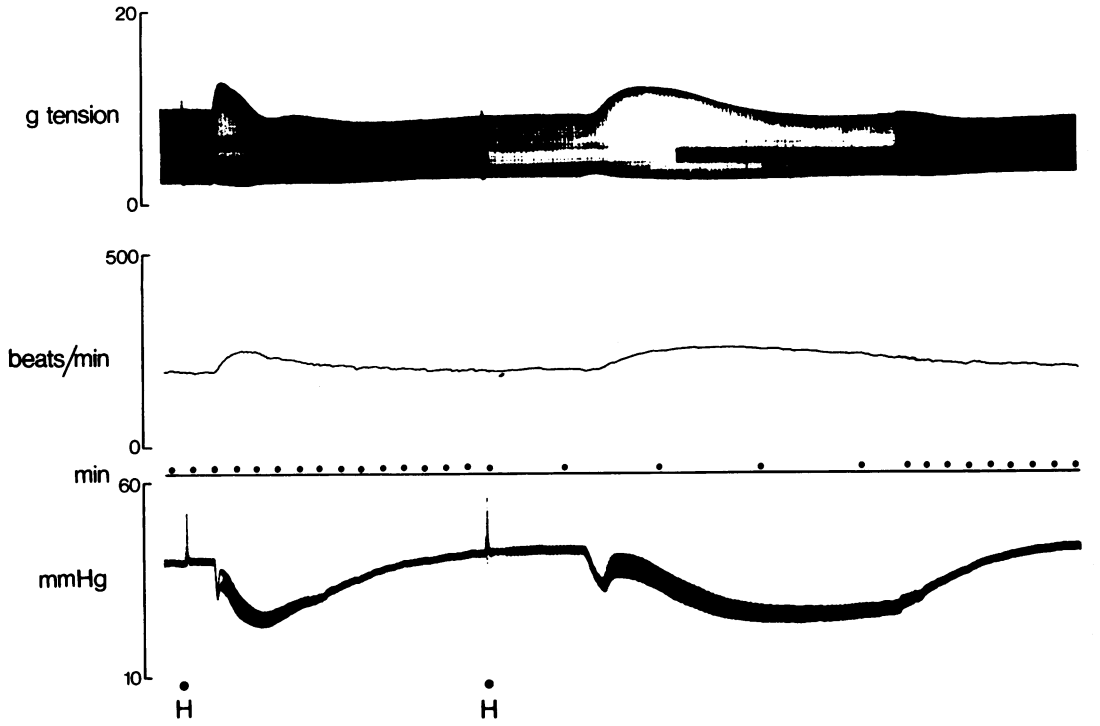

Figure 1 Guinea-pig isolated perfused heart. The effects of histamine (H, 1 μg) on the contractile force (upper record), heart rate (middle record) and coronary perfusion pressure (lower record). Administration was initially at a chart speed of 5 mm/min and repeated at 25 mm/min to separate the components of the vascular response.

and rate of contraction increased. The dose was repeated at a faster chart speed to separate three well defined phases of the coronary vascular response. These were: (a) An initial fall in perfusion pressure which preceded any effects on the force and rate of heart beat; (b) a secondary rise in pressure which commenced simultaneously with the onset of the positive inotropic and chronotropic responses. This component of the response was associated with more exaggerated excursions of the recorder stylus on either side of the mean pressure; (c) a fall in perfusion pressure which occurred while the heart was still excited, but continued after the force and rate of contractions had returned to normal. The coronary vascular response is therefore not a simple vasodilatation but consists of several components and the possible modification of each of these by the H_1- and H_2-receptor antagonists was next examined.

The initial coronary dilatation was antagonized by the inclusion of the classical antihistamine mepyramine (1 μg/ml) in the perfusion solution (Figure 2b). The increases in force and rate of contraction were unaffected and a biphasic coronary vascular response remained. This consisted of the rise in pressure coinciding with the onset of force and rate responses, followed by an unaltered predominant fall in perfusion pressure. Both these vascular responses were removed when the myocardial effects were abolished by the further introduction of the H_2-receptor antagonist burimamide (20 μg/ml) to the perfusion solution (Figure 2c).

When the order of administration of the antagonists was reversed (Figure 3), initial perfusion with burimamide (20 μg/ml) antagonized the myocardial effects of histamine, leaving a biphasic coronary vascular response (Figure 3b). The initial sharp fall in perfusion pressure was still present but was not followed by a rise in pressure; however, this was now accompanied by the myocardial effects previously observed prior to burimamide. Both of these components of the remaining response of the coronary circulation were antagonized by the addition of mepyramine (1 μg/ml) to the burimamide infusion (Figure 3c).

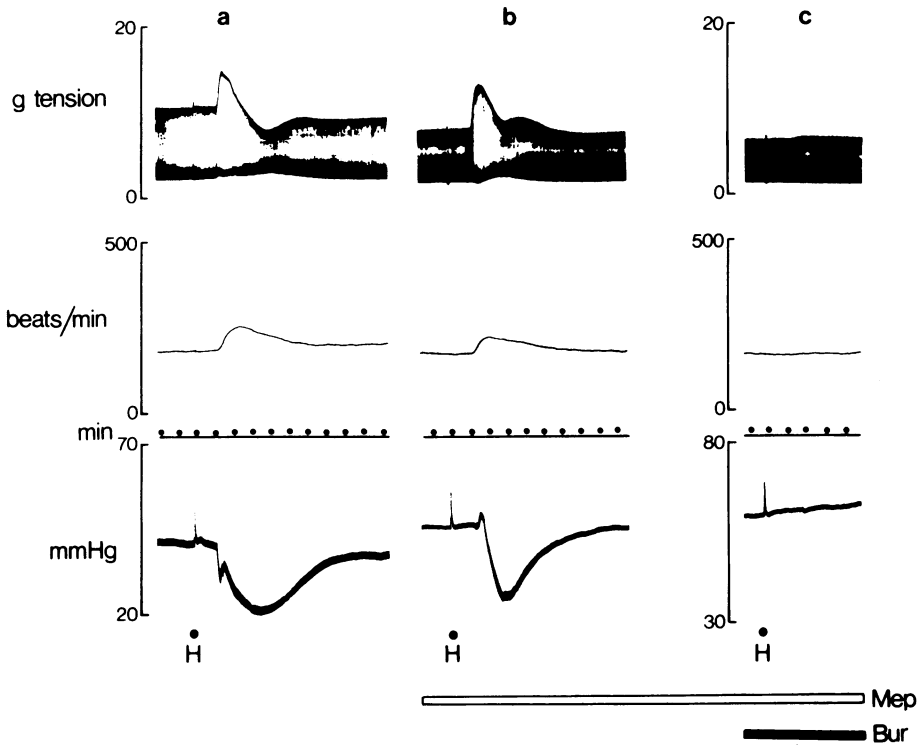

Figure 2 Guinea-pig isolated perfused heart. The effects of mepyramine alone (Mep, 1 μg/ml at open horizontal bar in (b) and combined with burimamide (Bur, 20 μg/ml) at solid horizontal bar in (c)) on the response of contractile force (upper record), heart rate (middle record) and coronary perfusion pressure (lower record) to histamine (H, 1 μg).

This figure also illustrates the rapid reversal of the burimamide blockade. Immediately after returning to a perfusion solution containing only mepyramine (Figure 3c), histamine was administered and the return of the force and rate responses began. Thereafter, the histamine dosage was repeated at regular intervals with complete restoration of the myocardial effects of histamine. Finally, the mepyramine was omitted, but even after 1 h of perfusion with this drug-free solution, the initial mepyramine-sensitive vasodilator response failed to return (Figure 3d), thus demonstrating the prolonged activity of mepyramine. The response of the coronary circulation at this point was characterized by the exaggerated excursions of the pen stylus during the rise in pressure. This differed from the rise in pressure seen before the mepyramine antagonism (Figure 3b) where only a smooth rise in pressure occurred with no change in pulse pressure. At the same time no myocardial effects were present.

Therefore two constrictor components of the coronary vascular response to histamine can be distinguished. The first is associated with a more pulsatile pressure trace and occurs concurrently with pronounced increases in force and rate on contraction. The second vasoconstriction is more delayed, has no increased pulse pressure and is present after blockade of the myocardial effects by burimamide. It is antagonized by mepyramine.

The investigation was next extended to the hearts of rabbits. Histamine (10 μg) produced positive inotropic and chronotropic responses and in the majority of preparations the coronary vascular response was biphasic, consisting of an initial rise in perfusion pressure followed by a more prolonged fall in pressure (Figure 4a). The positive chronotropic response to histamine was inhibited by burimamide (20 μg/ml), whereas the increase in tension was converted to a negative inotropic response. Histamine now caused only a vasoconstriction of the coronary circulation

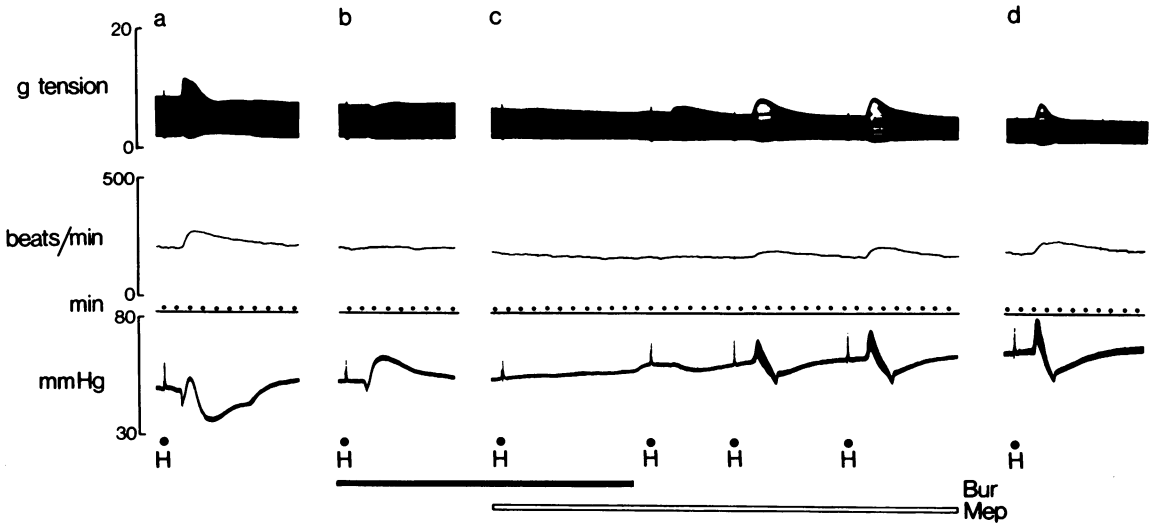

Figure 3 Guinea-pig isolated perfused heart. The effects of both addition and removal of burimamide (Bur, 20 μg/ml at solid horizontal bar) and mepyramine (Mep, 1 μg/ml at open horizontal bar) on the responses of the contractile force (upper record), heart rate (middle record) and coronary perfusion pressure (lower record) to histamine (H, 1 μg). The burimamide was omitted from the perfusion solution during (c) and in (d) histamine was repeated 1 h after perfusion with a drug-free solution.

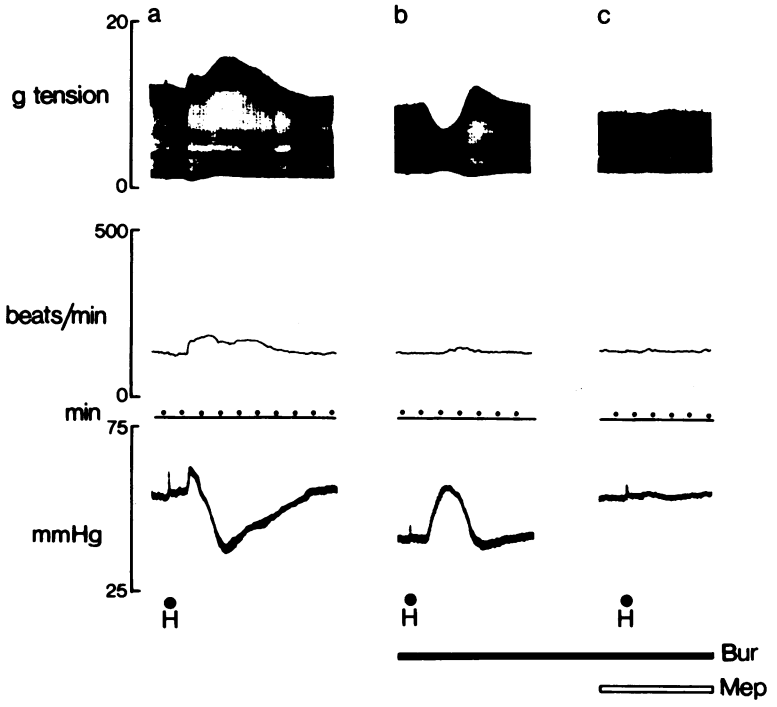

Figure 4 Rabbit isolated perfused heart. The effects of burimamide alone (Bur, 20 μg/ml at solid horizontal bar in (b)) and combined with mepyramine (Mep, 1 μg/ml at open horizontal bar in (c)) on the responses of contractile force (upper record), heart rate (middle record) and coronary perfusion pressure (lower record) to histamine (H, 10 μg).

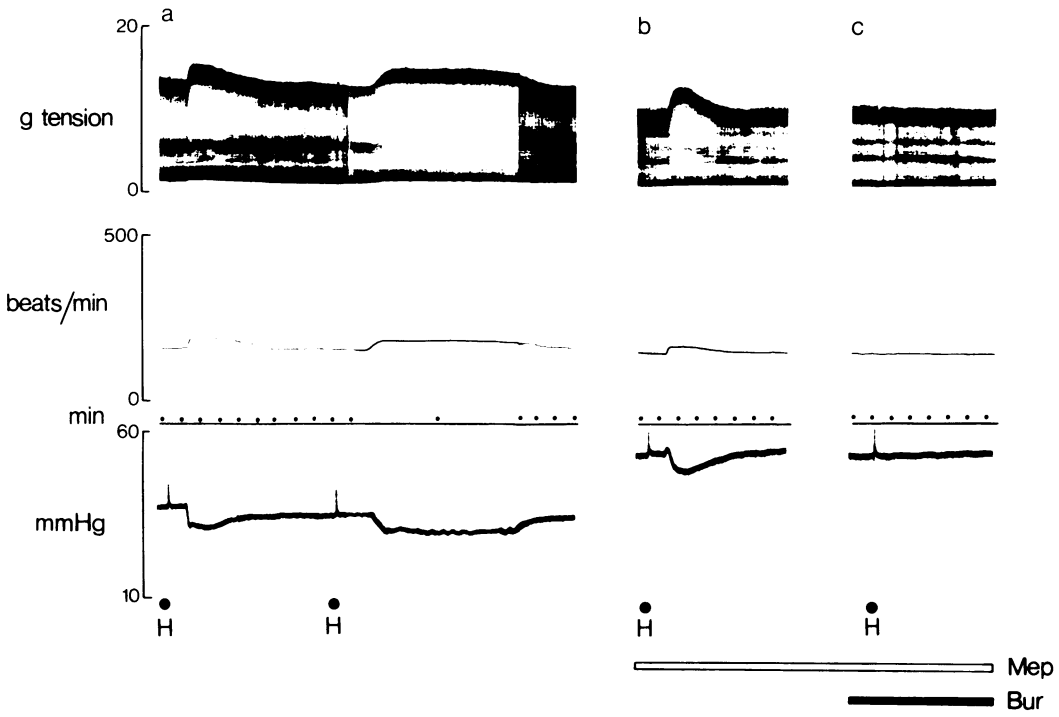

Figure 5 Rabbit isolated perfused heart. (a) Responses of the contractile force (upper record), heart rate (middle record) and coronary perfusion pressure (lower record) to histamine (H, 10 μg) at a chart speed of 5 mm/min and repeated at 25 mm/minute. (b) The effect of including mepyramine (Mep, 1 μg/ml at open horizontal bar) in the perfusion solution on the histamine responses. (c) The effect of both burimamide (Bur, 20 μg/ml at solid horizontal bar) and mepyramine on the responses to histamine.

(Figure 4b). This was abolished by the further introduction of mepyramine (1 μg/ml) as was the negative inotropic response (Figure 4c). In a few preparations there was no initial coronary vasoconstriction to histamine, instead, only a monophasic vasodilatation occurred. In these cases, a repeated dose of histamine at a faster chart speed revealed that the falls in perfusion pressure had followed the changes in force and rate of contraction (Figure 5a). This was therefore not comparable with the initial fall in pressure seen with guinea-pig hearts, which preceded any myocardial effects. Furthermore, it was not antagonized by mepyramine (Figure 5b). This coronary vascular response was abolished along with the myocardial responses by the secondary addition of burimamide (Figure 5c). Even in these rabbit hearts that exhibited solely vasodilator responses to histamine initially, only a vasoconstriction of the type seen in Figure 4b was present after the use of burimamide as the first antagonist.

The dose of histamine used in both species was submaximal, as confirmed by the preliminary construction of dose-response curves. These are plotted for guinea-pig hearts in Figure 6 before and during perfusion with burimamide (20 μg/ml). The tension and rate responses were measured as the increase to the peak effect (Figure 6a and b), and the total coronary vasodilatation was measured to the maximum fall in perfusion pressure (Figure 6c). Both the tension and rate responses were antagonized by burimamide and so too was the coronary vasodilatation. However, this coronary vascular response was divided into its component parts and the dose used throughout this study, 1 μg, was examined in more detail. The overall fall in pressure was clearly inhibited by burimamide but to a level that corresponded to the initial vasodilator component. When measured separately, this initial phase was unaltered and this fact is represented by the histograms in Figure 6d for the 1 μg dose of histamine.

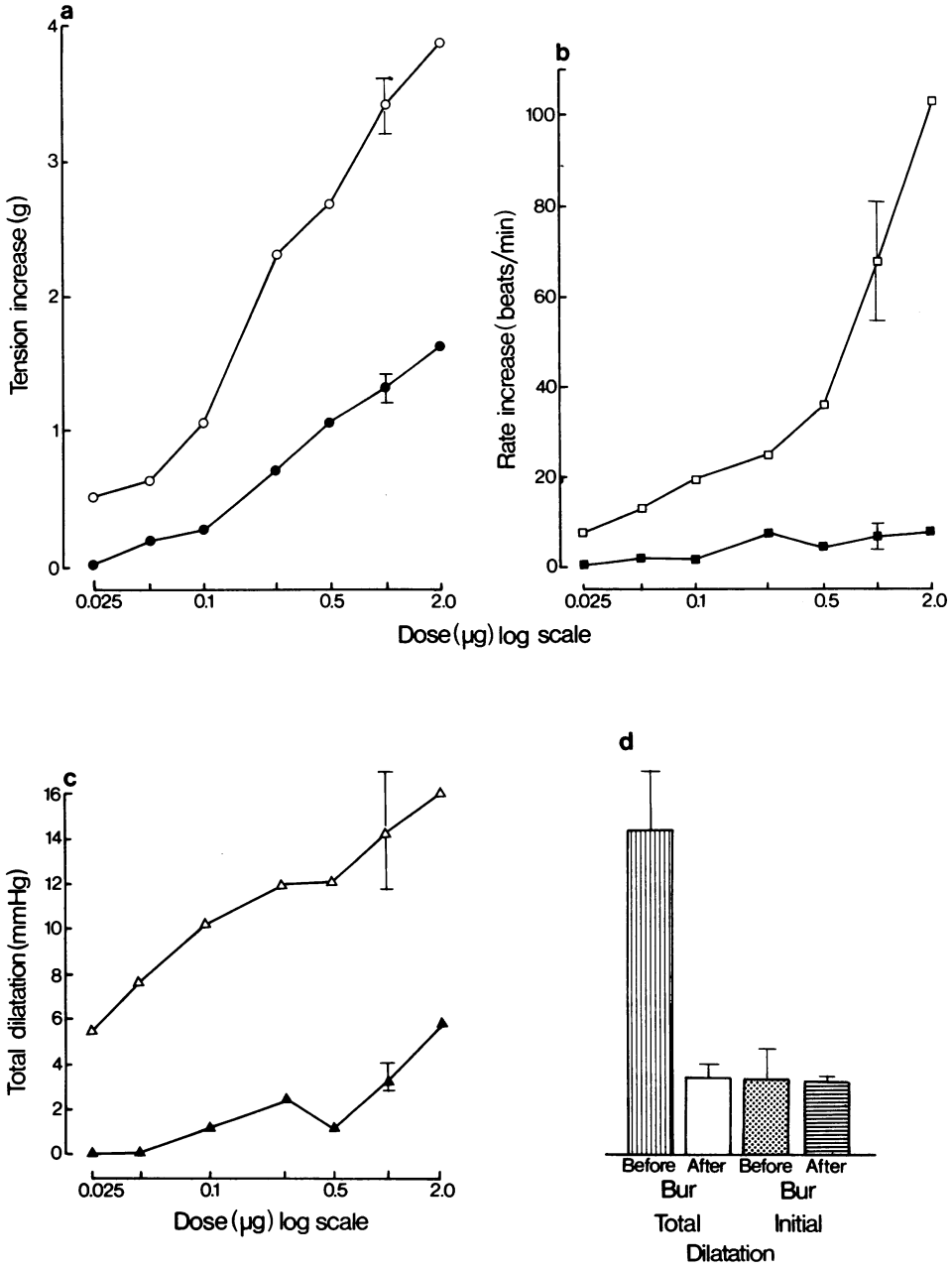

Figure 6 The effects of burimamide on the force, rate and coronary vascular responses of guinea-pig perfused hearts to histamine. Mean values were obtained from the same preparations. (a) Increase in tension in response to increasing doses of histamine before (○) and during (●) perfusion with burimamide (20 μg/ml). (b) Increase in rate in response to these doses of histamine before (□) and during (■) perfusion with burimamide (20 μg/ml). (c) Total fall in coronary perfusion pressure to the same increasing doses of histamine before (△) and during (▲) perfusion with burimamide (20 μg/ml). (d) Separation of the coronary vascular response to the 1 μg dose of histamine into the total fall in perfusion pressure before (vertical hatched column) and during (open column) perfusion with burimamide, and the initial rapid fall in perfusion pressure before (stippled column) and during (horizontal hatched column) burimamide perfusion (20 μg/ml).

Discussion

The stimulant effect of histamine upon the force and rate of cardiac contraction in both guinea-pig and rabbit hearts were not antagonized by the prototype antihistamine mepyramine. This confirms the previous observations of Trendelenburg (1960) and Bartlet (1963) that led to the classification of these effects as mediated via H_2-receptors (Black *et al.*, 1972; Ercan *et al.*, 1974; Levi & Kuye, 1974). However, these positive inotropic and chronotropic responses were antagonized by the H_2-receptor antagonist burimamide, as also shown by others (Black *et al.*, 1972; Capurro & Levi, 1973; Levi & Lee, 1974; McNeill & Verma, 1974b; Levi *et al.*, 1975). The antagonistic activity of burimamide was extremely short-lived and only persisted while the drug was present in the perfusion solution. The responses were rapidly restored to their original size on returning to a drug-free perfusion.

The overall effect of histamine on the coronary circulation *in vivo* and *in vitro* is one of vasodilatation, although this may depend upon the species (Parratt, 1968) and dose employed (Wégria, 1951; Charlier, 1961; Parratt, 1968). The predominant effect recorded here was a prolonged fall in perfusion pressure, indicative of vasodilatation. In guinea-pig perfused hearts, this vasodilatation has previously been shown to be blocked by the prototype H_1-receptor antagonists (Levi & Kuye, 1974). On the other hand, Ercan *et al.* (1974) have demonstrated blockade in the same species by the H_2-receptor antagonist metiamide along with the force and rate responses; although mepyramine was claimed to be ineffective. This conflicting evidence may well be explained by the separation here of the histamine-induced coronary vascular response of guinea-pig hearts into several well defined phases.

The first stage of the response was a fall in perfusion pressure occurring before the onset of any myocardial changes. Since this was antagonized by mepyramine, it is a direct effect on the coronary blood vessels due to vasodilatation mediated via histamine H_1-receptors. Therefore, in this respect, the results agree with those of Levi & Kuye (1974).

A secondary vasoconstrictor response commenced simultaneously with the increases in force and rate induced by histamine. It was accompanied in most preparations by exaggerated excurions of the recorder stylus and was only present when there were pronounced changes in force and rate of contraction. Therefore burimamide, in antagonizing these myocardial effects, also removed this component of the vascular response. Increases in force of contraction and tachycardia have variously been claimed to increase coronary flow indirectly by a massaging effect. (Wiggers, 1954) or to restrict flow by extravascular compression of the coronary vessels by the myocardium (Sabiston & Gregg, 1957). The latter phenomenon has received most favourable support and during drug-induced positive inotropic and chronotropic responses a greater resistance to flow can be expected. For example, a similar restriction in flow has been shown to accompany the force and rate responses to adrenaline in isolated perfused hearts (Melville & Lu, 1950; Douglas, Armengol & Talesnik, 1960). It is therefore suggested that this result of increases in the force and rate of the heart also applies to histamine, which produces a secondary vasoconstriction by a compressing effect on the coronary vessels by the myocardium. Its removal by burimamide is therefore merely a consequence of the blockade of the myocardial responses.

The fall in perfusion pressure that followed was longer lasting and is recognized as the predominant coronary effect of histamine in most species both *in vivo* and *in vitro* (Wégria, 1951; Charlier, 1961; Parratt, 1968). Its antagonism by burimamide compares with the findings of Ercan *et al.* (1974) using metiamide, who therefore assumed the presence of histamine H_2-receptors in the coronary vasculature. The dose-response curves to histamine clearly demonstrate this antagonism by burimamide of the overall vasodilatation. However, closer examination reveals that it is inhibited only to the level of the initial vasodilatation of the coronary vessels, mediated via H_1-receptors.

The appearance of the secondary fall in pressure only when significant changes in force and rate of contraction are produced by histamine and the fact that its magnitude was apparently proportional to the size of the cardiac responses suggests that the two effects are closely related. The occurrence of both biphasic coronary flow changes and biphasic rate responses also led Levi (1972) to deduce that they might be interdependent. The increase in myocardial activity may lead to the release of a metabolite that exerts a vasodilator effect on the coronary vasculature, which can outlast the changes in force and rate of contraction. Increases in myocardial activity are known to lead to a relative anoxia (Berne, 1958) which elicits a strong vasodilator action on the coronary circulation (Berne, 1964). Proposed mediators of this response to anoxia are the release of adenosine (Rubio & Berne, 1969) and prostaglandins (Kent, Alexander, Pisano, Keiser & Cooper, 1973; Wennmalm, Pham-Huu-Chanh & Junstad, 1974). These metabolites may therefore also be released by a relative anoxia

arising from increases in myocardial activity induced by histamine. Indeed, the overall coronary vasodilatation exerted by catecholamines has been attributed to the accompanying increased metabolic activity of the heart (Berne, 1964).

Histamine therefore exerts coronary vasodilatation by two mechanisms; a direct relaxation of coronary blood vessels mediated via H_1-receptors and a more predominant metabolically linked vasodilatation arising from the increased myocardial activity. The antagonism of the second component by burimamide is therefore a result of blockade of H_2-receptor-mediated myocardial effects and not of vascular H_2-receptors. This would contradict the conclusions of Ercan *et al.* (1974), although the existence of H_2-receptors in the coronary vasculature cannot be totally excluded by the present study.

The final component of the coronary vascular response to histamine is a vasoconstriction that is revealed after antagonism of the myocardial effects with burimamide. The myocardial stimulation normally produces vasoconstriction through extravascular compression. In addition, there is a vasoconstriction which follows the direct vasodilatation, and like the vasodilatation, is antagonized by mepyramine. It is therefore a direct effect on the coronary vasculature mediated via H_1-receptors and we can conclude that both vasoconstrictor and vasodilator effects are elicited by stimulation of H_1-receptors present in the coronary circulation of the guinea-pig.

The separation of the coronary vascular response of the guinea-pig isolated heart to histamine into four components may help to clarify the apparently anomalous results in the literature. One group of workers have antagonized the vasodilatation by mepyramine-like antihistamines (Levi & Kuye, 1974), whereas Ercan *et al.* (1974) failed to do so, but were successful with metiamide. The present study also revealed a failure to antagonize the gross vasodilatation with mepyramine, although the initial direct component was susceptible to blockade without significantly altering the overall size of the response. Close examination of the trace produced by Ercan *et al.* (1974) reveals a small inflection on the descending portion of the vasodilatation which may suggest the presence of the two vasodilator components that are clearly demonstrated in this paper; they however did not draw attention to this. The secondary direct vasoconstriction seen here only after burimamide was also sensitive to mepyramine. It is possible that removal of this component would effectively enhance the metabolically linked vasodilatation so masking any possible antagonism by mepyramine of the overall vasodilatation as claimed by Levi & Kuye (1974). However, if this were so, then the argument should apply equally to their experiments, and it does not alter the fact that the overall vasodilatation was not visibly antagonized by mepyramine. One conclusion is that different aspects of the histamine response have been recorded by the various experimental procedures. Levi & Kuye (1974) were possibly observing increases in coronary flow mediated predominantly by the direct effects on the coronary vasculature, whereas the responses in the present work and in that of Ercan *et al.* (1974) and Flacke *et al.* (1967) were predominantly indirect, resulting from the increased myocardial activity. It is also possible that the classical antihistamines used by Levi & Kuye (1974) were exerting some non-selective depressant effects both on the vasculature and on the myocardium thus reducing the metabolically-linked vasodilatation.

When the hearts of rabbits were examined, it was apparent that histamine failed to produce the initial direct vasodilatation mediated via H_1-receptors that was seen in guinea-pig hearts. Generally, biphasic coronary vascular responses were recorded, in which a constriction was followed by a more prolonged fall in pressure. Some hearts exhibited solely vasodilator responses, but these were unaffected by mepyramine and were converted to monophasic constrictor responses by burimamide. In fact all rabbit hearts produced purely constrictor responses after antagonism of the myocardial effects by burimamide. This was in turn blocked by mepyramine, indicating that it was a direct H_1-receptor effect on the coronary vessels.

At the same time as the direct vasoconstriction found in both rabbit and guinea-pig hearts during the burimamide antagonism, negative inotropic responses to histamine invariably occurred. It is unlikely that these were related either to the burimamide-resistant negative dromotropic responses that have been reported (Flacke *et al.*, 1967; Levi & Lee, 1974) or to the negative inotropic response seen *in vivo* and blocked by burimamide (Powell & Brody, 1973). In the present study it was antagonized by mepyramine at the same time as the removal of the constrictor response and is therefore probably a mechanical result of the constricted coronary vasculature.

Histamine therefore exerts only coronary vasoconstriction by interaction with H_1-receptors in the rabbit, which contrasts with the guinea-pig heart where both constriction and dilatation of coronary vessels occurs. Species differences have been reported elsewhere for other vascular beds. For example, the fall in blood pressure of the cat and dog due to histamine is mediated via both H_1- and H_2-receptors producing vasodilatation

(Parsons & Owen, 1973; Powell & Brody, 1973; Flynn & Owen, 1974); however, in the calf the vasodepressor response results from a balance between a vasodilator H_1-receptor and vasoconstrictor H_2-receptor stimulation (Eyre, 1973). The fall in blood pressure of the rabbit is the reverse, being due to a combination of H_1-pressor and H_2-depressor effects (Parsons & Owen, 1973). In the present study the rabbit also differs, since histamine exerts only H_1-receptor mediated coronary vasoconstriction. In the coronary vasculature, however, these direct effects of histamine are probably masked by the more pronounced effects of extravascular compression and metabolically induced vasodilatation resulting from the increased myocardial activity.

I am grateful to Dr R.W. Brimblecombe of SK & F Labs., Welwyn Garden City, for the generous gift of burimamide.

References

ASH, A.S.F. & SCHILD, H.O. (1966). Receptors mediating some actions of histamine. *Br. J. Pharmac. Chemother.*, **27**, 427-442.

BARTLET, A.L. (1963). The action of histamine on the isolated heart. *Br. J. Pharmac. Chemother.*, **21**, 450-461.

BERNE, R.M. (1958). Effect of epinephrine and norepinephrine on coronary circulation. *Circulation Res.*, **6**, 644-655.

BERNE, R.M. (1964). Regulation of coronary blood flow. *Physiol. Rev.*, **44**, 1-29.

BLACK J.W., DUNCAN, W.A.M., DURANT, G.J., GANELLIN, C.R. & PARSONS, M.E. (1972). Definition and antagonism of histamine H_2-receptors. *Nature, Lond.*, **236**, 385-390.

BROADLEY, K.J. (1970). An analysis of the coronary vascular responses to catecholamines, using a modified Langendorff heart preparation. *Br. J. Pharmac.*, **40**, 617-629.

CAPURRO, N. & LEVI, R. (1973). Anaphylaxis in the guinea-pig isolated heart: selective inhibition by burimamide of the positive inotropic and chronotropic effects of released histamine. *Br. J. Pharmac.*, **48**, 620-628.

CHARLIER, R. (1961). *Coronary Vasodilators.* Oxford: Pergamon Press.

DEWS, P.B. & GRAHAM, J.D.P. (1946). The antihistamine substance 2786 R.P. *Br. J. Pharmac. Chemother.*, **1**, 278-286.

DOUGLAS, R.C., ARMENGOL, V. & TALESNIK, J. (1960). Influence of cardiac activity on coronary flow control. *Acta physiol. latinoam.*, **10**, 205-216.

ERCAN, Z.S., BÖKESOY, T.A. & TÜRKER, R.K. (1974). A study of the histamine H_2-receptors in heart muscle and coronary vessels. *Eur. J. Pharmac.*, **27**, 259-262.

EYRE, P. (1973). Histamine H_2-receptors in sheep bronchus and cat trachea: the action of burimamide. *Br. J. Pharmac.*, **48**, 321-323.

FANTOZZI, R., LEDDA, F., MANNAIONI, P.F., MORONI, F. & MUGELLI, A. (1974). Definition of the antagonistic action of burimamide and metiamide on the positive inotropic effect of histamine in isolated heart preparations. *Br. J. Pharmac.*, **52**, 457-458P.

FLACKE, W., ATANACKOVIĆ, D., GILLIS, R.A. & ALPER, M.H. (1967). The actions of histamine on the mammalian heart. *J. Pharmac. exp. Ther.*, **155**, 271-278.

FLYNN, S.B. & OWEN, D.A.A. (1974). Vascular histamine receptors in the cat. *Br. J. Pharmac.*, **52**, 122P.

KENT, K.M., ALEXANDER, R.W., PISANO, J.J., KEISER, H.R. & COOPER, T. (1973). Prostaglandin dependent coronary vasodilator responses. *Physiologist*, **16**, 361.

LANGENDORFF, O. (1895). Untersuchungen am überlebenden Säugetierherzen. *Pflügers Arch. ges. Physiol.*, **61**, 291-332.

LEVI, R. (1972). Effects of exogenous and immunologically released histamine on the isolated heart: A quantitative comparison. *J. Pharmac. exp. Ther.*, **182**, 227-238.

LEVI, R., CAPURRO, N. & LEE, C.-H. (1975). Pharmacological characterization of cardiac histamine receptors: sensitivity to H_1- and H_2-receptor agonists and antagonists. *Eur. J. Pharmac.*, **30**, 328-335.

LEVI, R. & KUYE, J.O. (1974). Pharmacological characterization of cardiac histamine receptors: sensitivity to H_1-receptor antagonists. *Eur. J. Pharmac.*, **27**, 330-338.

LEVI, R. & LEE, C.-H. (1974). Characterization of cardiac histamine receptors by means of selective H_1 and H_2 agonists and antagonists. *Fedn. Proc.*, **33**, 585.

MANNAIONI, P.F. (1960). Interaction between histamine and dichloroisoproterenol, hexamethonium, pempidine and diphenhydramine in normal and reserpine-treated heart preparations. *Br. J. Pharmac. Chemother.*, **15**, 500-505.

McNEILL, J.H. & VERMA, S.C. (1974a). Blockade of cardiac histamine receptors by promethazine. *Can. J. Physiol. Pharmac.*, **52**, 23-27.

McNEILL, J.H. & VERMA, S.C. (1974b). Blockade by burimamide of the effects of histamine and histamine analogs on cardiac contractility, phosphorylase activation and cyclic adenosine monophosphate. *J. Pharmac. exp. Ther.*, **188**, 180-188.

MELVILLE, K.I. & LU, F.C. (1950). Effects of epinephrine, aminophylline, nitroglycerine and papaverine on coronary inflow and on heart contractions as recorded concurrently. *J. Pharmac. exp. Ther.*, **99**, 286-303.

PARRATT, J.R. (1968). Pharmacological aspects of the coronary circulation. In *Progress in Medicinal Chemistry*, ed. Ellis, G.P. & West, G.B., vol. **6**, pp. 11-66. London: Butterworth & Co. Ltd.

PARSONS, M.E. & OWEN, D.A.A. (1973). Receptors involved in the cardiovascular responses of histamine.

Proc. int. Symp. on Histamine H_2-Receptor Antagonists. pp. 127-136. Welwyn Garden City: Smith Kline & French Laboratories Ltd.

POWELL, J.R. & BRODY, M.J. (1973). Identification of two vascular histamine receptors in the dog. *Proc. int. Symp. on Histamine H_2-Receptor Antagonists.* pp. 137-150. Welwyn Garden City: Smith Kline & French Laboratories Ltd.

RUBIO, R. & BERNE, R.M. (1969). Release of adenosine by the normal myocardium in dogs and its relationship to the regulation of coronary resistance. *Circulation Res.*, **25**, 407-415.

SABISTON, D.C. & GREGG, D.E. (1957). Effects of cardiac contraction on coronary blood flow. *Circulation*, **15**, 14-20.

TRENDELENBURG, U. (1960). The action of histamine and 5-hydroxytryptamine on isolated mammalian atria. *J. Pharmac. exp. Ther.*, **130**, 450-460.

WÉGRIA, R. (1951). Pharmacology of the coronary circulation. *Pharmac. Rev.*, **3**, 197-246.

WENNMALM, Å., PHAM-HUU-CHANH & JUNSTAD, M. (1974). Hypoxia causes prostaglandin release from perfused rabbit hearts. *Acta physiol. scand.*, **91**, 133-135.

WIGGERS, C.J. (1954). The interplay of coronary vascular resistance and myocardial compression in regulating coronary flow. *Circulation Res.*, **2**, 271-279.

(Received February 10, 1975.
Revised May 21, 1975.)