EVIDENCE FOR BOTH H_1 AND H_2-HISTAMINE RECEPTORS IN RABBIT ATRIA*

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Summary: Spontaneously beating isolated atria of rabbits responded to histamine (0.5-16 $\mu g/ml$) with positive chrono-and inotropism. However, the inotropic response was greater than chronotropic one. The concentration-response curve of histamine for chronotropic effect was markedly shifted to the right in the presence of 0.5 $\mu g/ml$ metiamide (H_2-receptor antagonist), which *per se* augmented the control contractile amplitude in all the experiments. The rightward shift of chronotropic concentration response curve with mepyramine (H_1-antagonist) was, however, moderate. On the contrary, the inotropic concentration response curve of histamine was shifted to much greater extent to right with mepyramine (0.62 $\mu g/ml$) than with metiamide, thus suggesting a greater share of H_1 than H_2-receptors in the mediation of positive inotropic effect of histamine. The chronotropic effect appears to be mediated predominently by H_2-receptors. Unlike metiamide, mepyramine did not alter the spontaneous frequency or amplitude of contraction. The present study, thus lends support for dual histamine receptors in rabiit atria.

Key words: histamine, rabbit atria, H_1-receptors, mepyramine, H_2-receptors, metiamide

INTRODUCTION

Since the introduction of the compound burimamide (3), the previous classification of histamine receptors into H_1 and H_2 type (1), has gained further support. A large number of investigators (2,3,5,6,10,12,14,16,18,19,23,24) have reported that the increase in cardiac force of contraction is not blocked as well by H_1-receptor blocking agents like promethazine as by burimamide or other H_2-receptor antagonists, thus indicating mediation by H_2-receptor. Similarly, chronotropic effect of histamine was found to be antagonised by H_2-receptor antagonists in other studies (3,10,11).

Further studies have concluded that chronotropic effect of histamine on spontaneously beating right atria and inotropic effect on electrically driven left atria are mediated by H_2 and H_1-receptors, respectively (21,22,24).

Hughes and Coret (8) demonstrated the abolition of both positive ino- and chronotropic responses to histamine by promethazine (H_1-receptor antagonist) alone in spontaneously beating rabbit atria. However, these authors did not plot a dose-response curve and probably H_2-receptor antagonists, recently introduced, were not easily available, then.

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It would appear from the preceding literature that either histamine receptors in rabbit atrium are different from those in other species or as suggested by Hughes and Coret (8,9) promethazine affects both H_1 and H_2-receptors. In view of this controversy, the present study was undertaken to find out the nature of histamine receptors in spontaneously beating isolated atria of rabbit, employing both H_1 and H_2-receptor antagonists.

MATERIALS AND METHODS

The present study was conducted on 27 albino rabbits of either sex weighing 1-1.5 *kg*. The animals were sacrificed by cervical fracture and their hearts quickly removed and placed in oxygenated Tyrode solution. Both the atria were separated by excising all ventricular and extraneous tissues and were mounted in 25 *ml* organ bath, filled with fresh Tyrode solution and gassed constantly by a mixture of 95% O_2 and 5% CO_2 bubbling out from base of bath through sintered glass hook. The temperature and pH were maintained at 32°C and 7.4 respectively.

Spontaneous atrial contractions were recorded by a Starling's lever at 0.5 g tension and with 5-fold magnification, on smoked INCO kymograph at slow and fast speeds. The atria were allowed to equilibrate for one hr with frequent changes of bathing fluid and contractions recorded till there was no change of more than 5 beats, and a constant amplitude was obtained.

A cumulative concentration-response curve of histamine was obtained with stepwise rise in concentrations. Increasing concentrations were used when amplitude with preceding concentration became steady. The preparations were washed 18 times and then treated with either mepyramine 0.62 $\mu g/ml$ or metiamide 0.5 $\mu g/ml$ for half an hr and then a second cumulative concentration-response curve was obtained with repetition of previous concentrations of histamine while antagonists were still in the bath. Concentration response curves of adrenaline (A) and noradrenaline (NA) were also obtained in separate atria over the same concentration range as histamine.

All the drugs were added in a volume of 0.2 - 0.5 *ml* through a polyethylene tube of fine calibre, negotiated to the bottom of muscle chamber, and flushed by withdrawing equal volume of fluid from the bath. The drugs were prepared in 0.9% w/v NaCl at the time of experiment.

Drugs used: Histamine dihydrochloride (BDH), mepyramine maleate (May & Baker), metiamide (S.K. & F.), noradrenaline (Sigma), adrenaline tartrate (Bengal Chemicals) were used in the present experiments.

RESULTS

Histamine (0.5-16 $\mu g/ml$) produced graded positive chrono- and inotropic responses of the heart. The inotropic response was greater than the chronotropic. When the curves for inotropic versus chronotropic responses to histamine, adrenaline and noradrenaline were compared, it was observed that curve for histamine was shifted more to left in favour of positive inotorpism (Fig. 1).

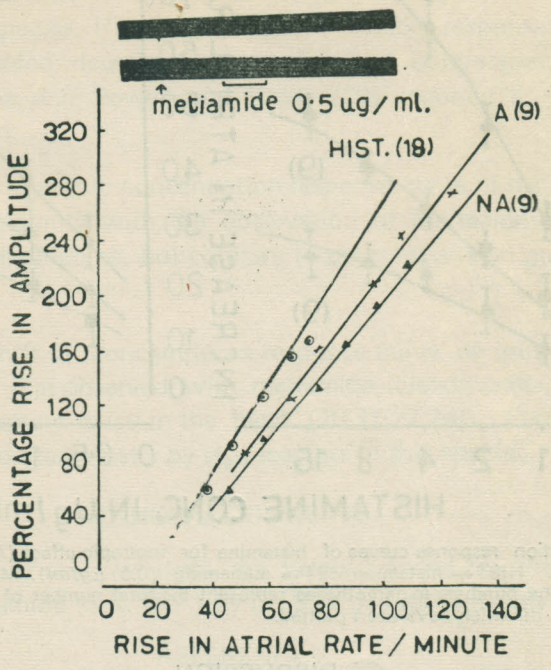

Fig 1 : The curves are for inotropic versus chronotropic responses to histamine (0.5-16 $\mu g/ml$), adrenaline (A) and nor-adrenaline (NA). The concentration of A or NA was the same as histamine. Note the shift of curve of histamine to the left in favour of inotropism.

The kymographic insertion at the top shows positive inotropic response to metiamide. Time mark is for one minute.

Metiamide (0.5 $\mu g/ml$) consistently produced a positive inotropic effect of its own ($25 \pm 6.5\%$; Fig. 1), through it hardly altered the control frequency. Mepyramine (0.62 $\mu g/ml$) did neither change the control amplitude nor the rate.

The inotropic concentration response curve of histamine was markedly shifted to right in the presence of mepyramine (0.62 $\mu g/ml$), but only moderately with metiamide (Fig. 2,A) The effect of the two antagonists on chronotropic concentration response curve of histamine was in reverse order as metiamide produced a much greater shift to right than mepyramine (Fig.2,B).

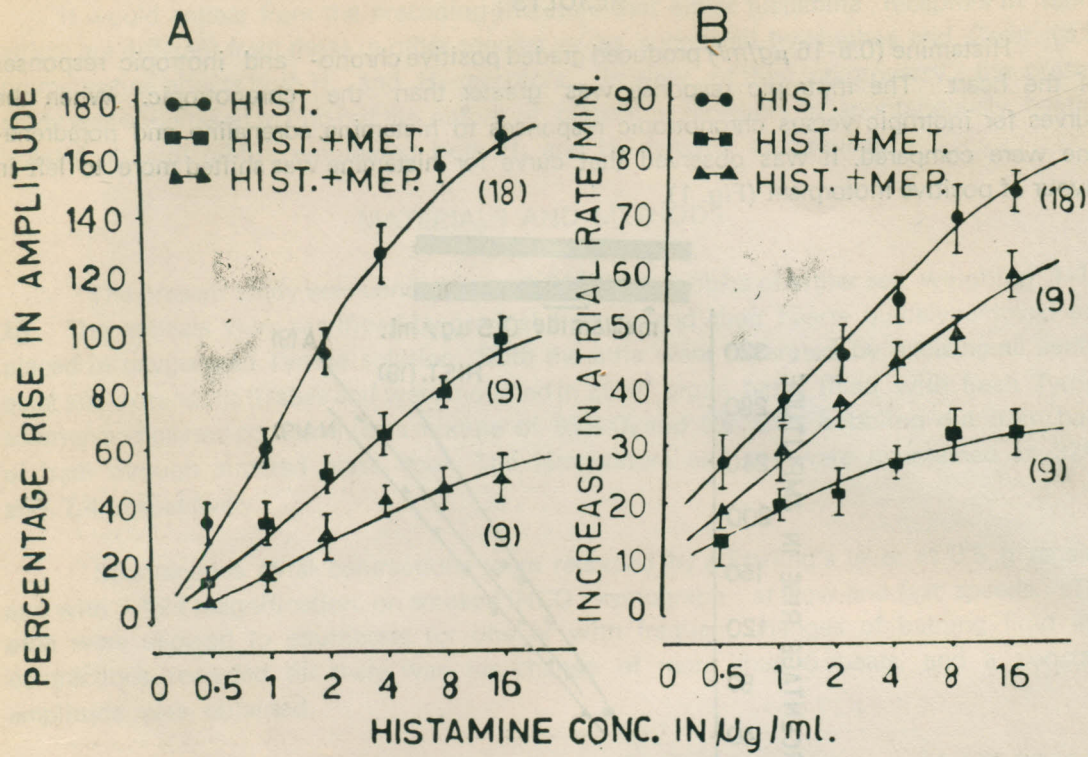

Fig. 2 : Concentration response curves of histamine for inotropic effect (A) and for chronotropic effect (B). HIST = histamine MET = metiamide (0.5 *µg/ml*), MEP = mepyramine (0.62 *µg/ml*). The numbers in parentheses represent the total number of observations, the mean and S.E.M. of which have been plotted.

DISCUSSION

A greater inotropic than chronotropic response to histamine observed in the present investigation is in agreement with the previous similar results reported by Dean (4) who observed linearly increasing positive ino- and chronotropic responses to histamine upto a concentration little beyond 10 *µg/ml* and then a steep fall upto 100 *µg/ml*. In the present study the maximum concentration of histamine was 16 *µg/ml* and till that level a linearly increasing response was observed.

Metiamide (0.5 *µg/ml*), a H_2-receptor antagonist, exerted a positive inotropic effect of its own which is also reported by Hood *et al.* (7). However, mepyramine (0.62 *µg/ml*), H_1-receptor antagonist, did not affect the frequency or contractility of atria.

The greater rightward shift of chronotropic concentration response curve with metiamide than mepyramine, partially confirms the earlier supposition that positive chronotropic

effect is mediated by H_2-receptors (3,10,11,21,22,24) because the moderate shift to right with mepyramine also would lend support to the possibility that H_1-receptors also mediate some chronotropism. Akin to this observation, Powell and Brody (20) have also reported blockade of chronotropic response to histamine with mepyramine. However, promethazine ($3x10^{-6}$ M) did not affect the chronotropic response to histamine in the right atria of guinea pig in another study (24), thus confirming the varying sensitivity of receptors to histamine antagonists in different species. Histamine produces variable responses in heart of different species; Bartlet (2) observed depression of amplitude of contraction of rat and domestic fowl heart with histamine and Powell and Brody (20) reported a similar depression of contractility of dog heart.

The greater shift of inotropic concentration response curve of histamine in the presence of mepyramine is in conformity with the observation of Mannaioni (13) for guinea pig atria made with diphenylhydramine, but contrary to other reports on guinea pig atria (5,10, 12,14-19,24).

Since rightward shift of concentration response curve of inotropic effect, produced by mepyramine exceeded that observed with metiamide, it lends credence to the proposition that both H_1 and H_2-receptors exist in the heart (20,21,22,24). Furthermore, it suggests that inotropic effect is mediated mostly by H_1-receptors in this species.

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