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Impromidine is a partial histamine H_2-receptor agonist on human ventricular myocardium

T.A.H. English*, R.W. Gristwood, D.A.A. Owen & J. Wallwork*

Department of Pharmacology, Smith Kline & French Research Ltd., The Frythe, Welwyn, Hertfordshire and Cardiac Transplant Unit*, Papworth Hospital, Papworth Everard, Cambridgeshire

1 The inotropic effects of impromidine have been studied and compared with those of histamine on human isolated left ventricular preparations stimulated at 1 Hz. Both drugs caused concentration-related increases in force of contraction and were of similar potency, although the maximum response to impromidine was markedly and significantly less than that to histamine.

2 The positive inotropic responses of impromidine were inhibited by cimetidine 1×10^{-5} M, consistent with histamine H_2-receptor involvement.

3 Impromidine 1×10^{-4} M inhibited maximal responses to histamine to a level equal to the maximal impromidine response; however, impromidine did not inhibit responses to isoprenaline.

4 Positive inotropic activity and inhibition of maximal responses to histamine occurred over a similar impromidine concentration-range.

5 Impromidine displaced histamine concentration-response curves to the right, whereas mepyramine had no effect on responses to histamine.

6 It is concluded that impromidine has positive inotropic activity on the human ventricle, that the response is mediated via histamine H_2-receptors, and that impromidine is a partial agonist compared with histamine.

Introduction

Histamine H_2-receptors, associated with both positive chronotropic and inotropic responses have been identified in the myocardium of guinea-pigs (e.g. Black *et al.*, 1972; Levi *et al.*, 1975; Flynn *et al.*, 1979). In contrast, studies in other species of laboratory animals have demonstrated substantial species variation in the sensitivity of the myocardium to histamine, in the nature of the response to histamine and in the receptors mediating the response (e.g. Levi *et al.*, 1982).

Histamine has been shown to be a positive inotropic agent on human, isolated ventricular myocardium (Eckel *et al.*, 1982). These inotropic responses to histamine were mimicked by the H_2-receptor agonist dimaprit and inhibited by cimetidine, consistent with involvement of histamine H_2-receptors in the response of the human myocardium to histamine.

Impromidine is a very potent and selective histamine H_2-receptor agonist (Durant *et al.*, 1978), which elicits increases in rate and force of contraction of guinea-pig hearts (Owen *et al.*, 1979; Bertaccini & Coruzzi, 1981). We have now investigated further the pharmacology of impromidine on human ventricular myocardium.

Methods

Left ventricular papillary muscle samples were obtained from 20 patients (12 male, 8 female) undergoing either open heart surgery (for mitral valve replacement, $n = 10$) or cardiac transplant (for reasons of congestive cardiomyopathy $n = 5$, or ischaemic heart disease $n = 5$). All patients had chronic cardiac failure (mitral valve replacements were clinical severity class II–IV, New York Heart Association classification; transplant recipients, class IV). All hearts were infused with a cardioplegic solution (St. Thomas' solution II) prior to excision of samples.

Immediately after excision, samples were placed in cool (0°C) Krebs solution (pre-equilibrated with 5% CO_2 in O_2, resulting pH 7.4) for transport from Papworth Hospital to Welwyn (duration approximately 1 h). In the laboratory, the papillary muscles were transferred to a dissection dish and cut into preparations (*ca* 0.1 cm × 0.7 cm) so that as far as possible muscle fibres ran parallel to the length of the preparation. Preparations were mounted vertically in 50 ml organ baths containing Krebs solution at 37°C. The base of the preparation was positioned between

point electrodes and the top attached to an isometric force transducer (Harvard 363). Tension was displayed on a polygraph (either Grass 79D or Devices M19). Preparations were placed under and maintained at 1 g resting tension and were electrically stimulated to contract at a physiological frequency of 1 Hz by rectangular pulses of 5 ms duration at 10% above threshold intensity (Palmer stimulator).

Preparations were allowed a period of at least 2 h to stabilize, during which the perfusion medium was replaced every 15 min. To compare the effects of histamine and impromidine, cumulative concentration-response curves were obtained to one of these (order at random), tissues were then washed, allowed at least 1 h to recover (washed at 15 min intervals), and then cumulative concentration-response curves were obtained to the second agonist.

Interactions between two drugs were investigated by incubating tissues for at least 10 min with one drug (agonist or antagonist) before exposure to the second drug.

Drugs

The following drugs were used: impromidine trihydrochloride (SK&F), cimetidine (SK&F), histamine acid phosphate (B.D.H.), mepyramine maleate (May & Baker) and isoprenaline sulphate (Sigma). All compounds except cimetidine were dissolved in Krebs solution. Cimetidine base was dissolved in a minimal volume of 0.1 N HCl, the pH raised to 6 by addition of 0.1 N NaOH and made up to volume with Krebs solution.

Statistical analysis

Statistical significance was tested using Student's *t* test for paired or unpaired data. A P value of <0.05 was considered significant.

Results

The mean resting force of contraction of preparations after stabilization was 91 ± 12 mg, $n = 20$. Histamine and impromidine both caused concentration-related increases in human ventricular myocardial contractility. The threshold concentrations for histamine and impromidine were similar at between 10^{-7} M and 10^{-6} M; however, the maximum responses caused differed markedly ($P<0.001$), see Figure 1. At 1×10^{-3} M the increases in force of contraction caused by histamine and impromidine were 137% ± 15% and 49% ± 11% above pre-drug control values respectively, $n = 17$.

Dividing the human tissues into subgroups related to aetiology of heart failure showed that impromidine caused a lower maximum response than histamine in all subgroups and no group differed significantly from the pooled mean value. Maximum responses, as a % of the histamine maximum, were 23.6 ± 8.6 congestive cardiomyopathy ($n = 5$), 33.6 ± 12.2 ischaemic heart disease ($n = 4$) and 34.3 ± 14.3 mitral valve disease ($n = 8$).

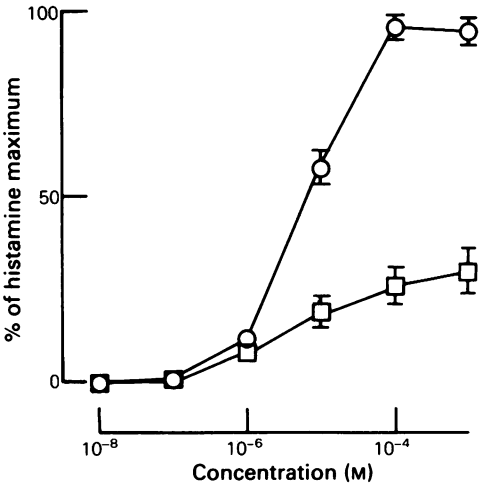

Figure 1 Increases in the force of contraction of isolated ventricular strips from human myocardium. Responses to histamine (○) and to impromidine (□) are expressed in terms of the maximum response to histamine. Points are means with s.e.mean shown by vertical lines, $n = 17$.

The positive inotropic response to impromidine was inhibited by treatment with cimetidine (Figure 2), the impromidine concentration-response curve being displaced to the right by cimetidine 1×10^{-5} M with a mean dose-ratio of 44 (range 20–53). Similar inhibition of responses to histamine by cimetidine in this preparation have been previously reported (Eckel *et al.*, 1982), cimetidine 1×10^{-5} M causing a mean dose-ratio of 28.

The lower maximum response to impromidine when compared with histamine suggested that impromidine might act as a partial agonist on H_2-receptors in human ventricular myocardium. This was examined by determining the inhibition, by impromidine, of responses to large concentrations of histamine.

In paired preparations, concentration-response curves to histamine and impromidine were obtained. When maximal responses to histamine had been established, addition of impromidine, 1×10^{-4} M to the preparations exposed to histamine caused a decrease in force of contraction to a value equal to the maximum achieved by impromidine alone (Figure 3). In contrast to the inhibition of response to histamine,

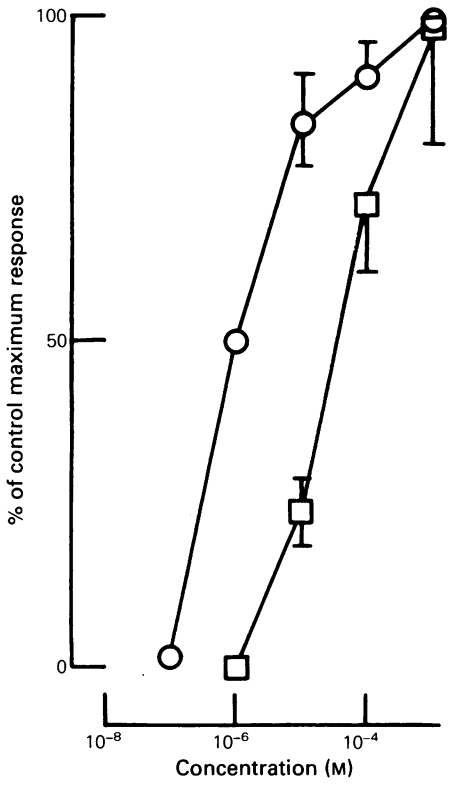

Figure 2 Inotropic responses to impromidine in isolated ventricular strips from human myocardium are inhibited by cimetidine, 1×10^{-5} M. Concentration-response curve prior to cimetidine-treatment (○), concentration-response curve in the presence of cimetidine (□). Points are means with s.e.mean shown by vertical lines, $n = 3$.

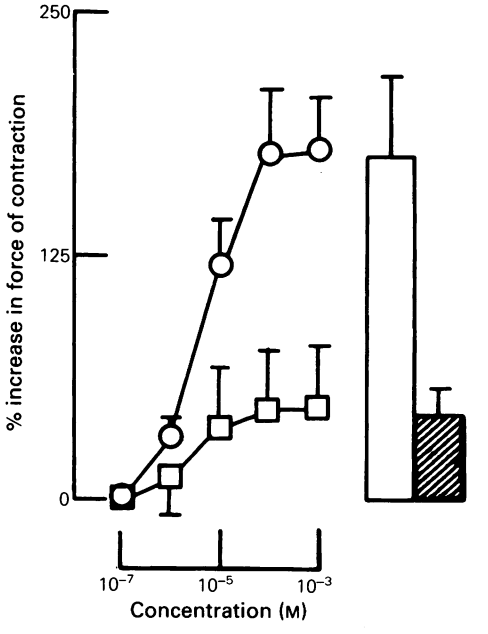

Figure 3 Impromidine inhibits responses to histamine in isolated ventricular strips of human myocardium. Concentration-response curves to histamine (○) and impromidine (□) were prepared simultaneously in paired preparations. Addition of impromidine, 1×10^{-4} M, to the top of the histamine concentration-response curve reverses the response to the maximal response caused by impromidine alone. The maximal response to histamine is shown by the open histogram, the hatched histogram shows the response in the same strips after addition of impromidine in the continued presence of histamine, 1×10^{-4} M. Values are means with s.e.means shown by vertical lines, $n = 3$.

impromidine, 1×10^{-4} M, had no significant effect on sub-maximal responses to isoprenaline. Isoprenaline, 1×10^{-7} M, alone increased force of contraction by 316% ± 98% before impromidine and when impromidine, 1×10^{-4} M was added on top of isoprenaline (1×10^{-7} M) force of contraction was increased slightly to 370% ± 105% above pre-drug control values, $n = 3$.

In another series of experiments the effects of impromidine 1×10^{-7} M to 1×10^{-3} M were studied on two preparations simultaneously, one untreated and one exposed to a maximal concentration of histamine (established as 1×10^{-4} M). The positive inotropic responses to impromidine when given alone developed over the same concentration-range as that which caused inhibition of the histamine response and the final inotropic responses, in the paired preparations, were similar (Figure 4).

In a further series of experiments, histamine concentration-response curves were repeated in the presence of impromidine 1×10^{-5} M. Impromidine, 1×10^{-5} M, increased the force of ventricular contraction and displaced the histamine concentration-response curve on ventricular preparations to the right (Figure 5), also consistent with the agonist and antagonist activity of a partial agonist.

Unlike impromidine, mepyramine at 1×10^{-7} M did not inhibit responses to histamine. Histamine at 1×10^{-4} M caused a 150% ± 65% increase in force of contraction, the response remained at 154% ± 69% following addition of mepyramine, $n = 3$.

Discussion

The present study has demonstrated that impromidine increases the force of contraction of human ventricular myocardium by acting as an agonist at H_2-

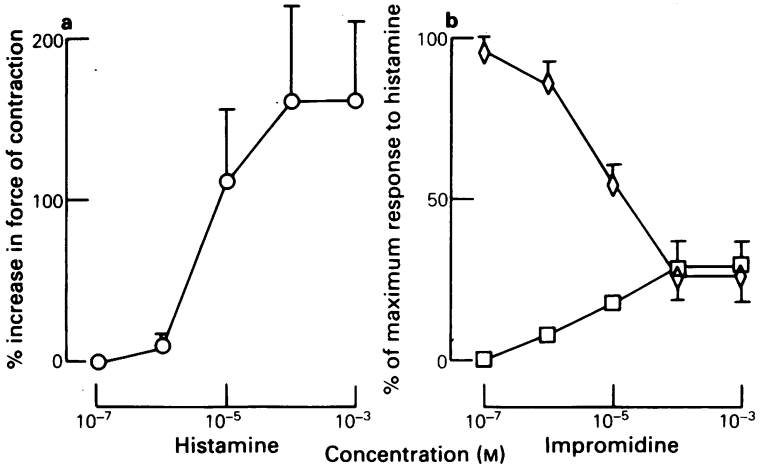

Figure 4 Interaction between histamine and impromidine on isolated ventricular strips from human myocardium. In (a), concentration-response curve to histamine (○) to establish maximal response. In (b), paired preparations were used to assess the responses to impromidine in untreated preparations (□) and in preparations exposed to histamine, 1×10^{-4} M, (◇). Values are means with s.e.mean shown by vertical lines, $n = 3$.

receptors. Thus, the concentration-response curve to impromidine was displaced to the right by cimetidine. Although only one concentration of cimetidine was employed, the dose-ratio obtained was consistent with that expected for action at H_2-receptors if it is assumed that cimetidine and impromidine are acting competitively for the receptor sites on the human myocardium.

A striking feature of the response to impromidine was that the maximum response was significantly less than the maximum response to histamine, a feature of compounds with partial agonist activity. Previous studies have shown that impromidine elicits a similar maximum response to histamine on guinea-pig atria (Durant *et al.*, 1978; Owen *et al.*, 1979), although the maximum effect on the ventricle was slightly, but significantly less for impromidine than histamine as assessed by measurement of left ventricular dp/dt_{max} in isolated working hearts (Owen *et al.*, 1979) or in isolated, ventricular strips (Bertaccini & Coruzzi, 1981). In neither of the guinea-pig studies was the lower maximum response to impromidine on the ventricle shown to be associated with the capacity of impromidine to inhibit maximal responses to histamine, a fundamental feature of partial agonism. Indeed, the maximum response to impromidine approached that to histamine so that demonstration of inhibition of maximal responses to histamine would have been technically very difficult. In the human ventricular myocardium the maximum response to impromidine was only approximately 30% of the histamine maximum, which allowed investigation of the H_2-receptor antagonist activity of impromidine. This has been clearly demonstrated.

Thus, addition of a large concentration of impromidine on top of a maximally effective concentration of histamine reversed the response to histamine to a level equal to the maximum which could be achieved by impromidine. This reversal of histamine by impromidine was shown to be selective, concentration-dependent and occurred over the same concentration-range as that which elicited an inotropic response in untreated preparations. Finally, impromidine, at a concentration that elicited a modest inotropic response itself, displaced the histamine concentration-response curve to the right and did so without reducing the maximum response to histamine.

The data derived in this study are all consistent with impromidine acting as a partial agonist at H_2-receptors on human ventricular myocardium. In addition to its activity at H_2-receptors, impromidine is a weak, competitive histamine H_1-receptor antagonist, pA_2 5.47 (Durant *et al.*, 1978). The role of H_1-receptors in the pharmacology of histamine reported on human ventricular myocardium can be discounted as mepyramine, an H_1-receptor antagonist, has no effect on responses to histamine in this preparation.

No precise quantitative comparison of the potencies of histamine and impromidine has been made in this study. However, it is clear that inotropic responses to both agents occur over the same concentration-range for each agonist and that the striking difference is in

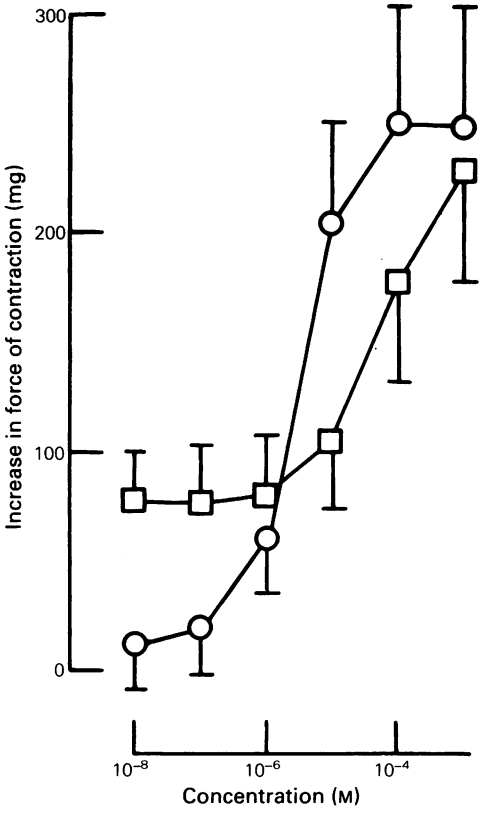

Figure 5 Inhibition of inotropic responses to histamine by impromidine in isolated ventricular strips from human myocardium. Histamine concentration-response curve before impromidine (○). Addition of impromidine, 1×10^{-5} M, caused a small inotropic response and displaced the histamine concentration-response curve to the right (□). Values are means with s.e.mean shown by vertical lines, $n = 3$.

the maximum response and not in the potency. This similar potency of histamine and impromidine is in contrast to the substantially greater potency of impromidine than histamine in a variety of other H_2-receptor systems. Thus, impromidine is 48 times more potent than histamine on guinea-pig isolated atria and approximately 20 fold more active as a gastric acid secretagogue in cats, rats and dogs (Durant *et al.*, 1978). The lower maximal response to impromidine relative to histamine seen in the present study has only been approached in one other preparation, the isolated whole stomach of the rat where the maximum response to impromidine is approximately 50% of the histamine maximum (Parsons & Sykes, 1980). In that system however, despite the low maximum response, impromidine was substantially, approximately 100 fold, more potent than histamine.

The presence of histamine H_2-receptors in human myocardium associated with positive inotropic activity (Eckel *et al.*, 1982), has prompted the proposal that H_2-receptor antagonists including impromidine might have a place in the treatment of severe cardiac failure (Baumann *et al.*, 1982). The present studies provide further evidence supporting the possible utility of impromidine in severe cardiac failure by demonstrating that this agonist can elicit a positive inotropic response in human ventricular myocardium. The tissue used has been obtained from patients with cardiac failure, i.e. from examples of the potential patient population. The finding that impromidine acts as a partial agonist on human ventricular myocardium is potentially advantageous to any proposed clinical use as this should provide assurance against the possible risk of overstimulation of the myocardium.

In conclusion, studies with impromidine on human left ventricular myocardium have demonstrated that the compound acts as a partial agonist. Impromidine causes positive inotropic responses but the maximum response is significantly less than the maximum response to histamine. Further, impromidine can act as an antagonist of histamine responses on the preparation.

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