Effects of histamine on human isolated heart muscle: comparison with effects of noradrenaline

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Histamine produces large changes in cardiac function in many animal species both in vivo and in vitro (for review see Owen 1977). The cardiac response to histamine in the guinea-pig in vitro includes increases in sinus rate, force of ventricular contraction and coronary flow (Bartlet 1963; Levi 1972; Flynn et al 1978), aortic flow, total cardiac output and external pressure—volume work (Flynn et al 1978) and increase in ventricular automaticity (Levi & Zavecz 1979). The above cardiac actions of histamine are all competitively antagonized by histamine H_2-receptor antagonists (Flynn et al 1979; Levi & Zavecz 1979) and therefore involve stimulation of histamine H_2-receptors. In contrast to the detailed data available for animal species little is known about the effects of histamine on the human heart.

We have investigated the effects of histamine on the human heart in vitro using right atrial biopsy samples obtained during cardiac surgery. After removal, the samples were placed immediately in Krebs solution at 4 °C then transferred to solution equilibrated with 5% CO_2 in O_2 at ambient temperature whilst transported to the laboratory. Right atrial trabeculae carneae 0·94 ± 0·03 cm × 0·103 ± 0·03 cm, were mounted vertically in a 15 ml organ bath containing modified Krebs solution (Flynn et al 1978) equilibrated with 5% CO_2 in O_2 at 37·5 °C. The base of the tissue was positioned between and in contact with a pair of short platinum electrodes and the top attached via a short length of cotton thread to a Statham UC3 transducing cell. This tissue which normally did not exhibit spontaneous contraction was placed under 1 g resting tension and electrically stimulated to contract with pulses of twice threshold voltage, 2 m s duration and frequency of 1 Hz using a Grass stimulator (model S4). Isometric tension was recorded on a Devices M19 recorder. Once set up preparations were allowed time to develop a stable contraction amplitude (approximately 45 min) during which the bath fluid was routinely changed by overflow at least every 5 min. The effects of histamine on contractility (tension amplitude) were compared with noradrenaline and the selective histamine H_2-receptor agonist dimaprit (Parsons et al 1977), by obtaining cumulative dose response curves to each agonist. Three dose-response curves were obtained in each preparation for this study with the agonist administration order assigned at random. Drug solutions were added to the bath in a volume not exceeding 0·1 ml and responses allowed to reach a stable maximum before increasing the bath concentration. After completion of dose response curves tissues were washed by overflow and allowed 15–30 min to recover. The effects of histamine receptor antagonists, cimetidine (H_2), mepyramine (H_1) or the adrenergic β-receptor antagonist propranolol on the histamine and noradrenaline responses were also investigated. For this study control dose response curves to histamine and noradrenaline in random order were first obtained in each preparation. The antagonist was then added to the perfusion medium and an equillibration period of at least 15 min allowed during which the bath fluid was changed at least every 5 min. The histamine and noradrenaline dose response curves were then repeated in the same order as that before antagonist administration. Four dose-response curves were thus obtained in each preparation for the antagonist study.

Drugs used were cimetidine (SK & F), dimaprit dihydrochloride (SK & F), histamine acid phosphate (BDH), mepyramine maleate (May & Barker), noradrenaline bitartrate (Chemie Linz AG) and propranolol hydrochloride (ICI).

Histamine at 10^{-7} M and above produced dose related increases in contractility as shown in Fig. 1. The maximum observed increase at 10^{-4} M represented a 126% ± 31% increase above control amplitude (n = 10). Noradrenaline produced similar dose-related increases in contractility (Fig. 1) and was approximately 3 × more potent than histamine. Dimaprit also produced similar responses to histamine and was less potent (Fig. 1). All three agonists produced similar

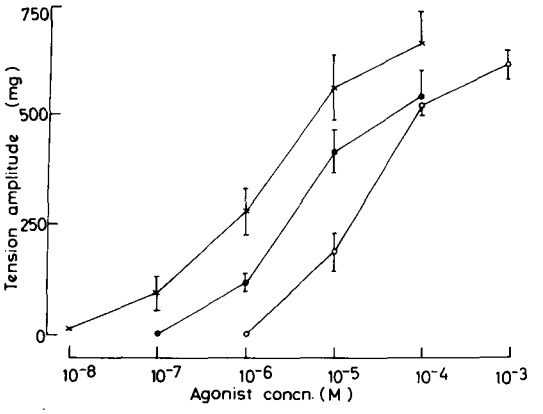

FIG. 1. Effects of histamine (●) (n = 10) noradrenaline (×) (n = 9) and dimaprit (○) (n = 4) on human right atrial contractility. Points are mean ± s.e., n indicates sample numbers. Ordinate: absolute increase in tension amplitude mg. Abscissa: agonist concentration (M).

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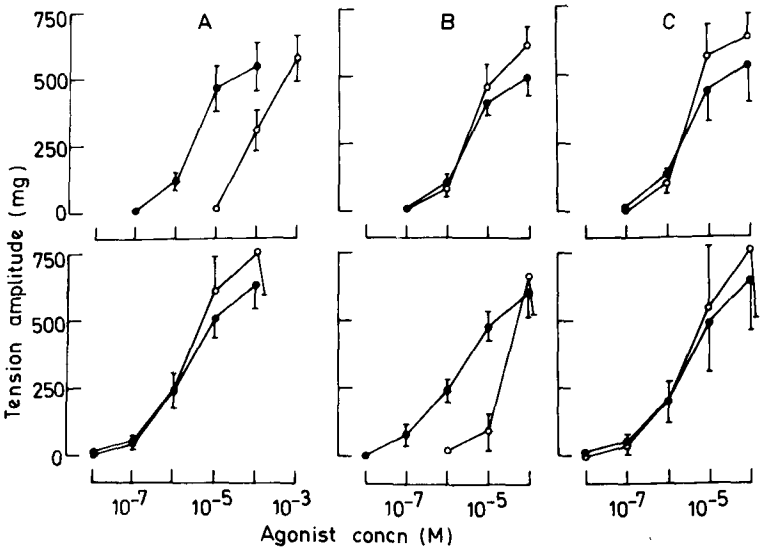

FIG. 2. Effects of histamine (upper graphs) and noradrenaline (lower graphs) on human right atrial contractility alone (●) and (n=5) in the presence of (A) cimetidine 10^{-5} M (○), (B) propranolol 10^{-6} M (n=4) or (C) mepyramine 10^{-7} M (n=3). Points are mean ± s.e., n indicates sample numbers. Ordinate: absolute increase in tension amplitude mg. Abscissa: agonist concentration (M).

maxima. The histamine dose-response curve repeated in the presence of cimetidine 10^{-5} M lay to the right of control indicating antagonism by cimetidine of the histamine response whereas the curves repeated in the presence of either mepyramine 10^{-7} M or propranolol 10^{-6} M were similar to control (Fig. 2). In contrast, the noradrenaline dose-response curve repeated in the presence of cimetidine was similar to control whereas the curve repeated in the presence of propranolol lay to the right of control, indicating antagonism by propranolol of the noradrenaline response (Fig. 2). The noradrenaline dose-response curve repeated in the presence of mepyramine like histamine was similar to control (Fig. 2).

In a number of preparations spontaneous contractions were produced by histamine, noradrenaline and dimaprit. The spontaneous rate was not quantified, however, the incidence of spontaneous activity, and the drug concentration at which it first occurred was noted. Histamine up to 10^{-4} M produced spontaneous activity in 7/24 (29%) preparations. Activity was first noted at 10^{-6} M in one (4%) preparation and by 10^{-5} M spontaneous activity has occurred in 5/24 (21%) preparations. Noradrenaline up to 10^{-4} M produced spontaneous activity in 9/19 (47%) preparations. Activity was first noted at 10^{-6} M in one (5%) preparation and by 10^{-5} M activity had occurred in 6/19 (32%) preparations. Dimaprit up to 10^{-4} M produced spontaneous activity in 1/4 (25%) preparations and this was at 10^{-5} M.

The results indicate that the human heart responds to histamine, which increases contractility and enhances atrial automaticity, with a sensitivity comparable to that for noradrenaline. The selective antagonism of the histamine contractility response by cimetidine indicates that this response is mediated via histamine H_2-receptors and not H_1 nor adrenergic β-receptors. The involvement of histamine H_2-receptors is confirmed by the similarity of the response to dimaprit. The production of spontaneous contractions by dimaprit suggests that the histamine-induced enhancement of atrial automaticity is also mediated via histamine H_2-receptors.

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REFERENCES

Bartlet, A. L. (1963) Br. J. Pharmacol. 21: 450–461

Flynn, S. B., Gristwood, R. W., Owen, D. A. A. (1978) J. Pharmacol. Methods 1: 183–195

Flynn, S. B., Gristwood, R. W., Owen, D. A. A. (1979) Br. J. Pharmacol. 65: 127–137

Levi, R. (1972) J. Pharmacol. Exp. Ther. 182: 227–238

Levi, R., Zavecz, J. H. (1979) Circ. Res. 44: 847–855

Owen, D. A. A. (1977) Gen. Pharmacol. 8: 141–156

Parsons, M. E., Owen, D. A. A., Ganellin, C. R., Durant, G. J. (1977) Agents Actions 7: 31–37