was specific (metabolites are not readily extracted by the procedure used, and no endogenous compounds gave retention times close to glyceryl trinitrate), reproducible, and sufficiently sensitive to determine concentrations of the drug as low as 500 pg ml^{-1} of plasma, with only a 200 μl sample of plasma. The retention times for glyceryl trinitrate and isosorbide dinitrate were 4·5 and 9·7 min respectively. Both peaks were symmetrical and no tailing was apparent. The g.l.c. characteristics of the deutero-glyceryl trinitrate were similar to those of the non-deuterated compound. Detector response was the same for glyceryl trinitrate and deutero-glyceryl trinitrate, and was linear up to 450 pg of glyceryl trinitrate. Reproducibilities of determination from rat plasma for 4 determinations of each were means of ±10·6% at 0·375 and ±10·4% at 0·75 ng glyceryl trinitrate/200 μl of plasma, and were ±3·2% at 3·75 and ±3·9% at 7·50 ng/200 μl of plasma. Recoveries from plasma were 75–80% and were not adversely affected by the addition of iodoacetamide.

The authors would like to thank Mr J. Roberts of Phase Separations Ltd., Queensferry for his expert advise and help in the preparation of the g.l.c. column, and to the Science Research Council for financial support for this work.

REFERENCES

Armstrong, P. W., Armstrong, J. A., Marks, G. S. (1979) Circulation 59: 585–588

Blake, M. I., Crespie, H. L., Katz, J. J. (1975) J. Pharm. Sci. 64: 367–391

British Pharmacopoeia (1973) p 220

De Nijs, R. C. M., Franken, J. J., Dooper, R. P. M., Rybs, J. A., De Ruve, H. J. J. M., Schutting, F. L. (1978) J. Chromatogr. 167: 231–241

Di Carlo, F. J., Melgar, M. D. (1970) Biochem. Pharmacol. 19: 1371–1379

Foster, A. B., Jarman, M., Stevens, J. D., Thomas, P., Westwood, J. H. (1974) Chem. Biol. Interact. 9: 327–340

Laurie, J. W. (1928) Glycerol and the glycols. Chem. Cat. Co., New York, p 377

Maier, G. A., Arena, C., Fung, H.-L. (1980) Biochem. Pharmacol. 29: 646–648

Yap, P. S. K., McNiff, E. F., Fung, H.-L. (1978) J. Pharm. Sci. 67: 582–586

J. Pharm. Pharmacol. 1981, 33: 246–247
Communicated November 10, 1980

0022–3573/81/040246–02 $02.50/0
© 1981 J. Pharm. Pharmacol.

Response of human ventricular heart muscle to histamine

ROBERT W. GRISTWOOD*, DAVID A. A. OWEN*, LOTHAR ECKEL**, PETER SATTER**, HERMANN NAWRATH†, *Pharmakologisches Institut der Universität Mainz, D-6500 Mainz, Federal Republic of Germany*

Histamine is present in large quantities in the heart and can significantly alter cardiac function (for review see Levi et al 1976; Owen 1977). Current evidence suggests that the effects of histamine on the heart are mediated by both, H_1- and H_2-receptors, the distribution and function of which seems to depend on species and region of the heart (Owen 1977). We have characterized the effects of histamine on action potential and force of contraction in human ventricular heart muscle. Histamine produced distinct changes of the action potential configuration and force of contraction which were blocked in the presence of cimetidine. The results are consistent with an increase of the calcium conductance at the myocardial cell membrane in response to H_2-receptor stimulation.

The effects of histamine on action potential and force of contraction were determined in human papillary muscles obtained from patients during cardiac surgery. Immediately after excision, the preparations were placed in cold (4 °C) oxygenated Tyrode's solution and carried to the laboratory. The time between excision and the beginning of the laboratory processing was about 90 min. In the laboratory, the muscles were transferred to a dissection chamber containing oxygenated Tyrode's solution and split into thin preparations so that the fibres ran parallel to the length of the strip. For recording electrical and mechanical activity, the preparations were mounted in a 1 ml organ bath which was continuously perfused with Tyrode's solution. One end of the preparation was connected to an inductive force displacement transducer by means of a stainless steel wire, and the other end was fixed to keep the muscle length as constant as possible. The Tyrode's solution was prepared with distilled deionized water and had the following composition (mM): NaCl, 136·9; KCl, 5·4; $MgCl_2$, 1·05; NaH_2PO_4, 0·42; $NaHCO_3$, 11·9; $CaCl_2$, 1·8; glucose, 5·6. The Tyrode's solution was continuously gassed with a mixture of 95% O_2 and 5% CO_2; the temperature was kept at 37·0 ± 0·2 °C. All muscles were driven electrically at 0·2 Hz by rectangular pulses of 1–5 ms duration (Grass stimulator and isolation unit; intensity 10–20% above threshold). Tension was recorded under isometric conditions at the apex of the preload active tension curve. The transmembrane potential was detected intracellularly by the use of 5–15 MOhm glass microelectrodes filled with 3 M KCl.

* Smith Kline and French Research Limited, Welwyn Garden City, Hertfordshire, England.
** Abteilung für Thorax, Herz- und Gefäßchirurgie, Klinikum der Johannes-Wolfgang-Goethe-Universität, D-6000 Frankfurt, Federal Republic of Germany.
† Correspondence.

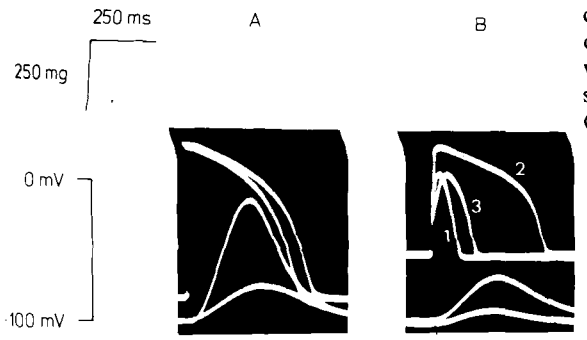

FIG. 1A. Action potential and force of contraction of a human papillary muscle under control conditions (inner action potential and lower contraction curve) and 10 min after the addition of histamine 10^{-5} M (outer action potential and upper contraction curve). Control and test records were superimposed. Histamine produced a prolongation of the action potential and a positive inotropic effect. B. Slow response (21·6 mM K^+) and force of contraction of a human papillary muscle elicited by supramaximal stimulus intensity under control conditions (1), 10 min after the addition of histamine 10^{-5} M (2), and 20 min after the addition of cimetidine 10^{-5} M (3). Control and test records were superimposed. Same preparation as in A. The histamine-induced changes of the slow response and the force of contraction were virtually abolished in the presence of cimetidine.

(For further details see Nawrath & Eckel 1979.) The drugs used were: histamine acid phosphate, BDH Biochemicals/London; cimetidine base, SK & F Ltd., Welwyn Garden City; propranolol hydrochloride, ICI-Pharma/Plankstadt.

A typical response of human ventricular myocardium to histamine is shown in Fig. 1A. Records under control conditions and in the presence of histamine 10^{-5} M were superimposed. Histamine increased both the duration and plateau height of the action potential and exerted a positive inotropic effect ($n = 6$). Time to peak tension and half maximum relaxation were shortened. Resting potential, dV/dt_{max} and overshoot were not significantly affected by histamine. The changes of both action potential configuration and force of contraction due to histamine 10^{-5} M were virtually abolished in the presence of cimetidine 10^{-5} M ($n = 3$). Responses to histamine were not affected by propranolol 10^{-6} M ($n = 3$).

Histamine may change the action potential configuration and the force of contraction by an increase of the calcium-dependent slow inward current. Fig. 1B depicts the original records of one experiment which was carried out with 21·6 mM K^+ in the Tyrode's solution (otherwise 5·4 mM K^+). Under these conditions (resting potential of −52 mV), the sodium conductance responsible for the fast upstroke of the action potential is virtually completely inactivated and calcium-dependent slow response action potentials can be recorded (originally described by Reuter & Scholz 1968). Histamine 10^{-5} M enhanced the height and duration of the slow response. In the presence of cimetidine 10^{-5} M the changes of both action potential configuration and force of contraction were virtually abolished.

The present investigation demonstrates that histamine changes action potential configuration and enhances the force of contraction in human ventricular heart muscle by interaction with H_2-receptors and that these effects are probably linked to an increase of the calcium dependent slow inward current during the cardiac action potential. The demonstration of histamine H_2-receptors on human ventricle compliments the previous evidence for H_2-receptors on human right atrium (Gristwood et al 1980a).

A physiological role of histamine in the heart appears unlikely, although endogenous histamine can contribute to changes in cardiac function including arrhythmias in guinea-pigs (Levi et al 1976; Gristwood et al 1980b). Since calcium-dependent slow response action potentials have been implicated in the genesis and/or perpetuation of cardiac arrhythmias (Cranefield 1975) it might well be that histamine release from the heart may initiate or sustain cardiac arrhythmias by such a mechanism in man.

We thank Mrs Petra Lauck for her skillful assistance.

REFERENCES

Cranefield, P. F. (1975) The conduction of the cardiac impulse. Mount Kisco, N.Y. Futura

Gristwood, R. W., Lincoln, J. C. R., Owen, D. A. A. (1980a) J. Pharm. Pharmacol. 32: 145–146

Gristwood, R. W., Owen, D. A. A., Smith, I. R. (1980b) Br. J. Pharmacol. 70: 105P–106P

Levi, R., Allan, G., Zavecz, J. C. (1976) Fed. Proc. 35: 1942–1947

Nawrath, H. Eckel, L. (1979) J. Cardiovasc. Pharmacol. 1: 415–425

Reuter, H. Scholz, H. (1968) Pflügers Arch. Ges. Physiol. 300: 87–107

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