A dual-component positive inotropic response of guinea-pig isolated atria to histamine

K.J. BROADLEY & C. WILSON

Department of Applied Pharmacology, Welsh School of Pharmacy, University of Wales Institute of Science and Technology, King Edward VII Avenue, Cardiff CF1 3NU

The positive chronotropic responses of the heart to histamine are mediated via H_2-receptors since they are antagonized by metiamide and burimamide (Reinhardt, Wagner & Schümann, 1974; Steinberg & Holland, 1975; Verma & McNeill, 1977). In paced preparations in which the rate response cannot interfere with the tension developed, the positive inotropic responses are antagonized by promethazine and tripelennamine and therefore mediated by H_1-receptors (Reinhardt *et al.*, 1974; Steinberg & Holland, 1975; Verma & McNeill, 1977).

We have further investigated the blockade of the histamine-induced positive inotropic and chronotropic responses of isolated guinea-pig atria by metiamide and mepyramine. Rate responses were obtained from the spontaneous right atria whereas tension responses were recorded from the paced left atria (2.0 Hz) set up at 38°C in Krebs-bicarbonate solution as described previously (Broadley & Lumley, 1977). Cumulative dose-response curves to histamine were constructed before and in the presence of metiamide (10^{-4} M) following a 30 min incubation period. Pre-antagonist curves were corrected for any sensitivity changes by performing control experiments ($n=4$). The rate dose-response curves were displaced to the right (dose ratio, 27.01 ± 13.12) whereas the tension curves were unaffected by metiamide. The rate, but not the tension, responses to histamine are therefore mediated by H_2-receptors. The tension responses of the spontaneous right atria were, however, displaced to the right, illustrating the contribution of rate changes to the tension of these preparations (Koch-Weser & Blinks, 1963).

Mepyramine (10^{-8} M) had no effect upon the tension dose-response curves. At 10^{-7} M, it produced a parallel rightwards shift of the tension curve (9.58 ± 3.83). There was, however, no further parallel shift by 3×10^{-7} or 10^{-6} M (6.28 ± 1.99 and 11.65 ± 3.60) although the maximum responses were reduced to 82.4 ± 7.3 and 84.1 ± 18.9 respectively. A mepyramine (H_1)-resistant component of the positive inotropic response therefore appeared to exist. The rate responses were unaffected by any of these mepyramine concentrations.

The possibility of two components to the tension response was further suggested by closer inspection of the dose-response curves which frequently revealed biphasic tension increases at some concentrations. Cumulative construction may therefore obscure the true qualitative character of the positive inotropic response. Histamine doses were therefore added sequentially, washing the bath when the maximum was attained at each dose. The biphasic tension increases were now more apparent. Unfortunately, in control experiments, considerable tachyphylaxis was found on repeating a second curve when using sequential administration; even with a 4-dose curve. This was avoided by using a lower bath temperature (25°C). Furthermore, the biphasic nature of the response was more marked, the primary and secondary components being separated by a negative phase. The primary response was antagonized by mepyramine (10^{-7} M), whereas the secondary component was unaffected, as was the rate response.

Admittedly the lower temperature may alter the histamine receptors (Kenakin, Krueger & Cook, 1974), but from either cumulative dose-response curves (38°C) or sequential single doses (25°C) there appear to be two components to the positive inotropic responses to histamine—an initial phase mediated via H_1-receptors and a secondary mepyramine-resistant component.

C.W. is an SRC CASE student. We are grateful to Smith, Kline & French, Ltd. for the metiamide.

References

BROADLEY, K.J. & LUMLEY, P. (1977). Selective reserpine-induced supersensitivity of the positive inotropic and chronotropic responses to isoprenaline and salbutamol in guinea-pig isolated atria. *Br. J. Pharmac.*, **59**, 51–60.

KENAKIN, T.P., KRUEGER, C.A. & COOK, D.A. (1974). Temperature-dependent interconversion of histamine H_1 and H_2 receptors in guinea-pig ileum. *Nature Lond.*, **252**, 54–55.

KOCH-WESER, J. & BLINKS, J.R. (1963). The influence of the interval between beats on myocardial contractility. *Pharmac. Rev.*, **15**, 601–652.

REINHARDT, D., WAGNER, J. & SCHÜMANN, H.J. (1974). Differentiation of H_1- and H_2- receptors mediating positive chronotropic and inotropic responses to histamine on atrial preparations of the guinea-pig. *Agents and Actions*, **4**, 217–221.

STEINBERG, M.I. & HOLLAND, D.R. (1975). Separate receptors mediating the positive inotropic and chronotropic effect of histamine in guinea-pig atria. *Eur. J. Pharmac.*, **34**, 95–104.

VERMA, S.C. & McNEILL, J.H. (1977). Cardiac histamine receptors: differences between left and right atria and right ventricle. *J. Pharmac. exp. Ther.*, **200**, 352–362.