SPECIES DIFFERENCES IN THE INOTROPIC EFFECTS OF HISTAMINE

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The positive inotropic effect of guinea-pig atria to a single submaximal dose (5.4×10^{-6}M) of histamine is biphasic in nature (Wilson & Broadley 1980). It consists of an initial positive inotropic effect mediated via H_1-receptors, followed by a negative component also mediated via H_1-receptors and finally, a more prolonged positive component that appears to be immune to both H_1 and H_2-receptor blockade (Wilson & Broadley 1980). In the present study we have compared the responses to histamine of the left atria of guinea-pigs, rats and rabbits. Left atria were suspended in Krebs-bicarbonate solution at 35°C, gassed with 5% CO_2 in oxygen and paced at a constant rate of 2Hz at threshold voltage + 50% and pulse width of 5 msec. Isometric tension was recorded. Histamine was added to the tissue either sequentially in single doses or cumulatively.

The biphasic response to histamine in guinea-pig atria was confirmed. In addition, when higher concentrations were added at the maximum positive inotropic response, this maximum developed tension was depressed. This negative inotropic effect was not related to the negative phase of the biphasic response at lower concentrations since it could not be antagonised by mepyramine. It was also unaffected by atropine.

The rat atria were relatively unresponsive to histamine, but exhibited a negative inotropic response at concentrations of 9.0×10^{-5}M and above. At 1.8×10^{-3}M this negative response was followed by a small increase in tension above the resting level. Neither component was antagonised by the H_2-antagonist metiamide (10^{-4}M), but the secondary effect was antagonised by mepyramine (10^{-6}M).

The rabbit atrium exhibited a dose-related monophasic positive inotropic response to histamine. This was unaffected by mepyramine but was antagonised by metiamide. The shift of cumulative dose-response curves was not parallel and the maximum was depressed by 10^{-5}M metiamide. In the presence of 10^{-4}M metiamide, no positive inotropic responses could be elicited; instead, dose-related negative responses appeared at the higher concentrations of histamine (9.0×10^{-4}M).

Therefore, high concentrations of histamine appear to exert negative inotropic effects in all three species that are not mediated via H_1 or H_2 receptors. Species differences occur, however, in the responses to lower concentrations. In the rat and guinea-pig, there is an H_1-receptor mediated positive inotropic effect, whereas in the rabbit the positive inotropic effect is H_2-receptor mediated. This latter finding is at variance with the observations of McNeill & Verma (1978). Only in the guinea-pig is there a negative component mediated via H_1-receptors and a positive component due to neither receptor type. This negative response has also been demonstrated in guinea-pig ventricular muscle (Zavecz & Levi 1978; Broadley & Wilson 1979).

This study has shown the importance of species selection and a knowledge of the receptor types involved when using isolated atria for the evaluation of histamine antagonists.

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