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Histamine responses mediated via H_1- and H_2-receptors in the isolated portal vein of the dog

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The effects of histamine were studied on the isolated circular muscle strip and longitudinal muscle strip of the dog portal vein. Histamine-induced contractions of the circular muscle were inhibited by H_1-receptor antagonist pyrilamine but increased by H_2-receptor antagonist ranitidine. When the tissues were contracted with $PGF_{2\alpha}$ in the presence of pyrilamine, histamine produced the relaxation of the circular muscle but not longitudinal muscle. The relaxation of the circular muscle was inhibited by ranitidine in a concentration dependent manner, the pA_2 value for ranitidine being 6·97 (6·55–7·39). It is concluded that the response of the circular muscle to histamine is the sum of two components, H_1-receptor mediated contraction and H_2-receptor mediated relaxation.

Helical strips of the isolated portal vein of the rabbit have vigorous spontaneous activity and respond to histamine with contraction (Sutter 1965; Hughes & Vane 1976; Cook & Macleod 1978). Since the portal vein is composed of two smooth muscle layers—an outer longitudinal and inner circular layer, a comparison of the responsiveness to histamine of the circular and longitudinal strips of the rabbit portal vein was made by Brown et al (1982), who observed that histamine produced contractile responses of similar amplitude in the two layers. However, in strips of dog portal vein we had previously observed a smaller contractile response to histamine of the muscle layer than of the longitudinal circular muscle layer (Shimo et al 1972). Recently Konishi et al (1981) demonstrated histamine-induced relaxations of isolated helical strips from a variety of dog arteries and concluded that these relaxations were mediated through histamine H_2-receptors. The present studies demonstrate the presence of histamine H_2-receptors within the circular muscle layer of the dog portal vein and suggest that the smaller contractile response of this layer is due to an interaction between H_1-receptors mediating contraction and H_2-receptors mediating relaxation.

Methods

Mongrel dogs of either sex, 10–15 kg, were killed with an overdose of sodium pentobarbitone (i.v.). immediately after the death of the animal, a segment of the portal vein was dissected and placed in oxygenated Krebs-Ringer solution. The strips of the circular or longitudinal muscle layer were prepared according to Brown et al (1982) and suspended in 10 ml organ baths containing modified Krebs-Ringer solution (Composition (mM): NaCl 120, KCl 4·7, $CaCl_2$ 2·5, $MgCl_2$ 1·2, $NaHCO_3$ 25, KH_2PO_4 1·2 and Glucose 14: pH 7·4) aerated with 5% CO_2 in oxygen at 37 °C. The Krebs-Ringer solution contained 2 μM prazosin hydrochloride, an α_1-adrenoceptor antagonist to block any adrenergic component of the histamine-induced response (Flacke et al 1967; Sarantos-Laska et al 1983). The preparation was mounted under a 0·5 g load and allowed to equilibrate for at least 60 min before the start of experiment. Responses of the preparations were recorded on an ink-writing oscillograph using isotonic transducers (Nihon Kohden). The dose response relationships for contractions or relaxations to histamine were obtained by adding histamine cumulatively. Contractile effects of histamine were measured as a percentage of the response of the tissue to 30 mM potassium chloride and relaxant effects were expressed as percent inhibition of the prostaglandin $F_{2\alpha}$ (3 μM)-induced contraction. The data obtained were expressed as mean ± s.e. cumulative concentration-response curves. pA_2 values for the antagonists, pyrilamine and ranitidine, were calculated from Arunlakshana & Schild (1959) plots.

Drugs used were: aminophylline, atropine sulphate, histamine dihydrochloride, potassium chloride, prazosin hydrochloride, propranolol hydrochloride, prostaglandin $F_{2\alpha}$, pyrilamine maleate, ranitidine hydrochloride. All drugs were dissolved in physiological saline.

Results and discussion

The longitudinal muscle strip shows vigorous rhythmic movement while the circular muscle strip has little or no spontaneous activity. In the circular muscle strips, histamine (1–100 μM) caused dose-dependent contractions which were antagonized by the histamine H_1-receptor antagonist pyrilamine (3 nM–30 nM). The cumulative concentration-response curves to histamine were shifted to the right in parallel and the pA_2 value calculated for pyrilamine was 8·89 (8·82–8·96, n : 6). These results indicate that the contractile response to histamine is mediated via histamine H_1-receptors. On the other hand, the H_2-receptor antagonist ranitidine (0·1 mM), which is about 5 times more potent than cimetidine in guinea-pig atrium and rat uterus and is highly specific for H_2-receptors (Daly et al 1981) augmented these contractions and shifted the cumulative concentration-response curves to the left in parallel (Fig. 1). These observations suggested that the circular muscle might contain histamine H_2-receptors through

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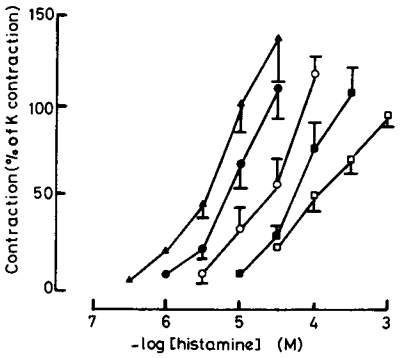

FIG. 1. Cumulative concentration-response curves for contraction of the isolated circular muscle strip of the dog portal vein in histamine in the absence (●) and presence of the H_1-receptor antagonist pyrilamine 3 nM (○), 10 nM (■) and 30 nM (□), and in the presence of ranitidine 0·1 mM (▲). The contraction induced by 30 mM potassium chloride was taken as 100%. All experiments were conducted in the presence of the α_1-adrenoceptor antagonist prazosin (2 μM). Each point represents the mean of 8 preparations. Vertical lines show s.e.m.

which relaxation to histamine might be mediated. Therefore, the relaxant effect of histamine was investigated on circular muscle in Krebs solution containing the H_1-receptor antagonist pyrilamine (1 μM). Since the circular muscle preparation is devoid of tone, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$ 3 μM) was used to contract the muscle. During the $PGF_{2\alpha}$-induced contraction, histamine (0·1–10 μM) produced relaxations of the circular muscle (Fig. 2), but had no significant effect on longitudinal muscle strip in concentrations up to 10 μM. Fig. 2 shows cumulative concentration-response curves

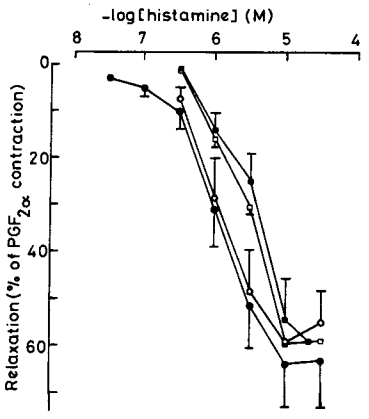

FIG. 2. Cumulative concentration-response curves for relaxation of the isolated circular muscle strip of the dog portal vein by histamine in the absence (●) and presence of ranitidine 30 nM (○), 0·1 μM (□) and 0·3 μM (■). Relaxations to histamine were demonstrated as a reduction in the maximal contraction induced by $PGF_{2\alpha}$ (3 μM) in the presence of pyrilamine (1 μM) and prazosin (2 μM). Each point is the mean of 5 preparations. Vertical lines show s.e.m.

Table 1. pA_2 values for the histamine H_1- or H_2-receptor antagonists against histamine.

Antagonists	n	pA_2 (Means with 95% confidence limits)	Slope of Schild regression
Pyrilamine	6	8·89 08·82–8·96)	−0·80
Ranitidine	5	6·97 (6·55–7·39)	−0·96

n is the number of experiments.

for the relaxant effect of histamine. At concentrations above 0·1 μM, histamine produced relaxations of the circular muscle and elicited a maximal response (63·0 ± 10·4%, n = 5) at 30 μM. These concentration-response curves for histamine-induced relaxations in the presence of pyrilamine were shifted to the right in a parallel, dose-dependent manner by ranitidine (30 nM–0·3 μM) and could be abolished by ranitidine at 100 μM. These results suggest that ranitidine and histamine compete at the histamine H_2-receptors in this tissue. The pA_2 value for ranitidine and the slope of the Schild plots, are shown in Table 1. The pA_2 value was 6·97 (6·55–7·39, n = 5) which is consistent with the value obtained in the guinea-pig isolated atrium (Daly et al 1981). The value of the slope (−0·96) was not significantly different from unity and therefore, is compatible with an antagonism of a competitive nature.

The relaxations induced by histamine were not significantly modified by atropine (0·1 μM), propranolol (1 μM), or the adenosine receptor antagonist and phosphodiesterase inhibitor, theophylline (30 μM).

From these observations it is concluded that the circular muscle layer of the isolated portal vein of the dog contains both H_1- and H_2-receptors and that the response of this tissue to histamine is the sum of two components, H_1-receptor mediated contraction and H_2-receptor mediated relaxation.

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