Histamine receptors in the gastric microcirculation

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SUMMARY The types and functions of histamine receptors in the submucosal arterioles of the corpus and antrum of the cat and rat stomach were studied using an in vivo microscopy technique. Change in arteriolar diameter in response to superfusion of histamine with and without antagonists was measured by an image-splitting technique. H₁ and H₂ histamine receptors subserving vasodilatation were demonstrated in both the antral and corpus submucosal arterioles of the cat and rat. However, the H₂ effect was predominant in the antrum (the H₂ antagonist inhibited histamine dilatation only in the presence of the H₁ antagonist), while H₁ and H₂ effects were approximately equal and independent in the corpus.

Histamine plays a major role in a number of physiological processes throughout the body, including the regulation of blood flow. It acts via two types of receptors; first, those blocked by mepyramine—for example, the receptors mediating bronchial constriction—termed H₁ (Ash and Schild, 1966), and, second, those not blocked by mepyramine—for example, the receptors mediating gastric secretion—termed H₂ (Black et al., 1972). The recently developed H₂ antagonists (Black et al., 1972) block the latter receptors. The two types of histamine receptor antagonists have been used to study the distribution and function of histamine receptors in different vascular beds. H₁ receptors subserving vasoconstriction and H₂ receptors subserving vasodilatation were found in the rabbit ear artery (Glover et al., 1973; Parsons and Owens, 1973) while only H₂ receptors subserving vasodilatation were found in the human temporal artery (Glover et al., 1973). Both H₁ and H₂ receptors subserving vasodilatation were observed in the general circulation—that is, depression of systemic arterial blood pressure—of the dog (Powell and Brody, 1973, 1976) and cat (Parsons and Owen, 1973), in the skeletal muscle of the dog (Powell and Brody, 1973, 1976) and in the intestinal circulation of the cat (Guth and Smith, 1978). When both receptors subserved vasodilatation, the H₁ receptor effects predominated—that is, an H₂ effect could not be demonstrated unless the H₁ receptor was blocked.

The purpose of the present investigation was to determine the types and function of histamine receptors in the submucosal arterioles of the corpus and antrum of the stomach of the cat and rat.

Methods

Cats weighing between 2 and 4 kg and male Sprague Dawley rats weighing between 150 and 200 g were used throughout this study. The animals were fasted but allowed free access to water for 24 hours before study. An in vivo microscopy technique was used to study gastric submucosal arteriolar responses (Guth and Rosenberg, 1972). The animals were anaesthetised with sodium pentobarbital, 35 mg/kg intraperitoneally, the abdomen opened, and the stomach exteriorised. For visualisation of the antrum a clad fibreglass rod was passed into the stomach through a small incision in the duodenum. For visualisation of the corpus, the rod was passed into the stomach through a small incision high in the fundus of the cat stomach or in the rumen of the rat stomach. The gastric wall was then transilluminated by passing light from a high intensity light source through this rod. Using a compound microscope with long working distance objectives, the microvascular bed was visualised. For optimum visualisation of the submucosal vascular network, it was necessary carefully to remove serosal and muscle layers from a small area of either the corpus or antrum thus exposing the submucosal plexi to direct viewing. The flow of blood through the submucosal arteriolar arcades to the mucosal arterioles and the capillary bed at the base of the mucosa and then back from the mucosa through collecting venules and into the submucosal
venular network could clearly be seen. The area under study was continuously superfused with a Krebs solution at 38°C. Body temperature was monitored and maintained between 37 and 38°C by a heating pad. An image-splitting recording technique was used to monitor submucosal arteriolar diameter changes (Baez, 1966).

For study of histamine and the histamine antagonists, the compounds were added to the superfusing fluid so that the submucosal vascular network was continuously bathed with solutions of known molarity. The concentrations employed were: histamine 10^{-4}M, mepyramine, an H_{1} antagonist, 10^{-8}M, and metiamide, an H_{2} antagonist, 10^{-4}M. Previous studies revealed these were the optimally effective concentrations of mepyramine and metiamide (Guth and Smith, 1978). Higher concentrations of these agents by themselves inhibited noradrenaline vasoconstriction. While histamine produced readily measurable, marked dilatation of the rat corpus submucosal arterioles, the dilatation of cat and rat antral arterioles and cat corpus arterioles was relatively small. In order to amplify this effect so that the antagonists could be more readily studied, the antral submucosal bed in the cat and rat and the corpus bed in the cat were superfused with noradrenaline 10^{-8}-10^{-7}M in order partially to constrict the arterioles. Subsequent superfusions with histamine with and without the antagonists contained noradrenaline. Six to 10 minutes were allowed between superfusion episodes to permit effects of the previously superfused agents to wear off. During these intervals superfusion with the Krebs solution alone was maintained. Repeat superfusions with histamine were performed at the end of each series of studies to be certain that the histamine response had not changed. To ascertain whether the H_{1} and H_{2} antagonist effects were specific for histamine, similar studies were performed with another vasodilator, papaverine 10^{-8}M.

The paired t test was used for statistical analysis of the results.

Results

Corpus

Results of the microcirculatory studies in the corpus of seven cats are presented in Fig. 1. The size of the arterioles studied was similar in all cats, averaging 36-0 ± 2-9 μm (mean ± SE, before noradrenaline constriction). Histamine caused dilatation in all animals, averaging 72-8 ± 8-9% above control diameter. Both the H_{1} antagonist and the H_{2} antagonist partially inhibited this response in all animals. The average diameters were 31-2 ± 8-1 and 44-2 ± 7-3% above control with the H_{1} and H_{2} antagonists respectively. These were significantly less than the histamine dilated diameter (p<0.01). When the antagonists were given together, there was complete inhibition of the histamine effect, the diameter being 5-6 ± 7-4% above control (not significantly different from 0). The effects of the antagonists appeared to be additive: 31-2% dilatation due to H_{2} effect + 44-2% dilatation due to H_{1} effect = 75-8% dilatation together (and histamine alone yielded 72-8 ± 8-9% dilatation).

Results of the microcirculatory studies in the corpus of seven rats are presented in Fig. 2. Vessels of similar size to those in the cat were studied, 32-9 ± 2-6 μm. Again dilatation occurred in all rats, the arteriolar diameter increasing on average to 36-1 ± 5-1% above control. Both H_{1} and H_{2} antagonists inhibited the histamine dilatation in all animals studied and this inhibition was statistically significant (p<0.01). Interestingly, H_{2} receptor antagonism alone nearly completely inhibited the response, the diameter being only 6-2 ± 3-6% above control. However, the H_{1} antagonist alone also markedly inhibited the histamine effect, the average diameter being 10-8 ± 3-2% above control. The two antagonists together also completely inhibited the effect of histamine.
**Histamine receptors in the gastric microcirculation**

Fig. 2  *Rat corpus*: mean percent increase in submucosal arteriolar diameter in response to histamine and the histamine antagonists. Values are means ± SE of seven animals. ** significantly smaller than histamine-induced dilatation (H) at $p<0.01$ (paired $t$ test).

Fig. 3  *Cat antrum*: mean percent increase in submucosal arteriolar diameter in response to histamine and the histamine antagonists. Values are means ± SE of six animals. ** significantly smaller than histamine-induced dilatation at $p<0.01$ (paired $t$ test).

**Antrum**

Results of microcirculatory studies in six cats are presented in Fig. 3. The arterioles studied averaged $54.6 ± 7.8 \mu m$ in diameter. Histamine produced arteriolar dilatation in all animals ($46.3 ± 11.8\%$ above control). The H$_1$ antagonist partially but significantly ($p<0.01$) inhibited this response in all animals, the dilatation now averaging only $17.3 ± 10.6\%$ above control. The H$_2$ antagonist alone had no effect on the histamine response in any cat, but, when administered with the H$_1$ antagonist, there was complete inhibition of the histamine effect. The inhibition in the presence of both antagonists was significantly greater than with the H$_1$ antagonist alone ($p<0.05$, paired $t$ test).

Results obtained in six rats are presented in Fig. 4. The arterioles studied averaged $32.7 ± 2 \mu m$ in diameter. Histamine produced arteriolar dilatation in all six rats studied ($48.8 ± 11.4\%$ above control). The H$_1$ antagonist significantly, and nearly completely, inhibited this response ($p<0.05$), dilatation now averaging $12.7 ± 10.1\%$ above control. The H$_2$ antagonist alone had no effect and, when administered with the H$_1$ antagonist, it did not significantly increase the inhibition obtained with the H$_1$ antagonist alone (the difference in diameter between H + H$_1$A and H + H$_1$A + H$_2$A was not statistically significant).

**Specificity of histamine antagonists**

The effect of the histamine antagonists on papaverine induced dilatation of corpus submucosal arterioles was studied in five cats. Papaverine produced a $45.2 ± 7.5\%$ dilatation of the noradrenaline constructed arterioles. The H$_1$ and H$_2$ antagonists, separately or together, had no effect on the papaverine induced dilatation.

**Discussion**

The results of the present investigation indicate a distinct difference in the behaviour of histamine receptors on the submucosal arterioles of the antrum and corpus. In both regions the H$_1$ and H$_2$ receptors subserve vasodilatation. However, in the antrum the receptors behave in a fashion similar to that found in the small intestine submucosal arterioles (Guth and Smith, 1978). The H$_1$ receptor antagonist partially inhibited histamine dilatation and the effect of the H$_2$ antagonist could not be demonstrated unless the H$_1$ receptor was blocked. This was clear in the cat antrum (Fig. 3) but not in the rat antrum studies (Fig. 4) where, because of the nearly complete inhibition by the H$_1$ antagonist, an H$_2$ effect was not demonstrable. The predominance of H$_1$ receptors when both receptors subserve vasodilatation has also been found in skeletal muscle and the general circulation when the depressor effect of histamine was studied (Parsons and Owen, 1973; Powell and Brody, 1973; Powell and Brody, 1976). In the corpus, on the other hand, independent H$_1$ and H$_2$ receptor effects could be demonstrated (see Figs. 1 and 2). To date, similar independent H$_1$ and H$_2$ receptor effects have not been observed in any other vascular bed where both receptors subserved vasodilatation. In the cat studies, these effects were additive. In the rat studies, the inhibition by either antagonist was so marked that interpretation of the effect of the two antagonists administered together
was difficult. The more marked effect of the H₁ and H₂ antagonists alone seen in the rat study might be due to the smaller histamine effect seen in the rat without noradrenaline constriction, 36·1% dilatation, than in the cat with noradrenaline constriction, 72·8% dilatation.

The corpus and antrum perform different functions. The secretion of acid is a major function of the corpus. Histamine is an important stimulant of acid secretion. H₂ receptors on the parietal cell are responsible for this function of histamine. While an increase in mucosal blood flow will not stimulate acid secretion, an increase in flow is essential to meet the increased metabolic needs of the actively secreting parietal cell. Marked inhibition of mucosal blood flow will diminish acid secretion (Jacobson et al., 1966). Therefore, a direct histamine effect on submucosal arterioles would not be unexpected. It is of interest that H₁ and H₂ receptors independently subserving vasodilatation were demonstrated on these arterioles. Since all stimuli of acid secretion increase mucosal blood flow (probably via vasoactive catabolites from the parietal cell), it is difficult to separate gastric secretory and primary blood flow effects using standard flow measurement techniques. For example, Jacobson and Chang (1969), found that both histamine and gastrin increased gastric mucosal blood flow, as determined by aminopyrine clearance, in the dog. However, the ratio of gastric mucosal blood flow to acid secretory rate was greater for histamine than for gastrin. This suggested, but did not prove, that the increased flow due to histamine represented both a direct pharmacological vasodilating effect and an indirect metabolic effect secondary to secretion. In previous studies we have shown that the gastric submucosal arterioles are the major resistance vessels regulating blood flow to the gastric mucosa (Guth and Smith, 1975). When these constrict, mucosal flow decreases, when they dilate, flow increases. Thus the effect of histamine on H₂ receptors on the parietal cell to increase acid secretion would simultaneously call forth an increase in blood flow to these cells via the dilating effect of H₂ as well as H₁ receptors on the corpus submucosal arterioles.

The concentrations of mepyramine and metiamide employed in this study were chosen on the basis of maximum inhibition of histamine-induced vasodilatation without that concentration of the antihistamine having any vasoactive effect by itself. The pA₂ for mepyramine is approximately 9 (Arun-lakshana and Schild, 1959) and for metiamide approximately 6 (Black et al., 1973). Therefore, relatively 100 times higher concentrations were used for mepyramine than for metiamide. Lower concentrations were not studied. Nevertheless the specificity of the agents in these concentrations for histamine receptor blockade was demonstrated by their failure to affect papaverine-induced vasodilatation.

The precise meaning of the interaction between H₁ and H₂ receptors in the antrum and other vascular beds in which the vasodilating effect is 'predominantly' an H₁ effect is not clear. It has been postulated (Powell and Brody, 1973) that this may be due to (1) a greater number of H₁ receptors, (2) greater affinity of histamine for H₁ receptors, or (3) greater smooth muscle action as a result of H₁-receptor activation. Blockade of the dominant H₁ receptor is hypothesised to be necessary 'to allow the H₂ receptor to become more dominant and allow for a nearly pure H₂-response'. Perhaps studies with the recently available pure H₁ and H₂ antagonists will shed some light on this question.
Histamine receptors in the gastric microcirculation

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P H Guth and E Smith

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