Sensitivity of the parietal cell and gastric microvasculature to histamine and histamine antagonists in the dog

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Gastric acid output and mucosal blood flow (GMBF) increase in parallel during stimulation but the increased GMBF has been assumed to be due to increased parietal cell metabolities (Holton, 1973). Since the discovery that both histamine H_1- and H_2-receptors subserve vasodilatation in a variety of species it has been postulated that GMBF as well as acid secretion might be regulated via release of mucosal histamine (Gerkens, Flexner, Oates & Shand, 1977). The purpose of the present investigation was to study the sensitivity of both the parietal cell acid output and the gastric microvasculature to histamine, alone and in combination with H_1- and H_2-receptor antagonists, in the conscious dog.

Four female dogs with chronic Heidenhain pouches were used. Acid secretion and mucosal blood flow were measured simultaneously. Acid output was collected in 15 min samples by pouch perfusion with saline and titrated to pH 7.4 with NaOH (0.1 M) using an automatic titrator (Radiometer, Copenhagen) and secretion expressed in μmoles H^+/min. GMBF (ml/min) was estimated using the Neutral Red clearance marker technique (Knight & McIsaac, 1977).

A dose-response study was first done in each dog using histamine alone (7 doses: $0.31–97.8 \times 10^{-8}$ mole $kg^{-1}h^{-1}$). Each dose was given by intravenous infusion for one hour. The dose-response study was repeated with the additional infusion of either mepyramine (2.5×10^{-6} mole $kg^{-1}h^{-1}$) or one of three doses of cimetidine (2.5, 5, or 10×10^{-6} mole $kg^{-1}h^{-1}$), beginning the antagonist infusion one-half hour before the histamine.

Statistical analysis of the data was as follows: for construction of dose-response curves the acid output and GMBF were taken as the mean of the 3rd and 4th 15 min periods in each hour. The experimental data were fitted to logistic curves for histamine alone and in combination with antagonists. Maximal output for acid secretion and GMBF, and the Km (agonist dose giving half maximal output) were then calculated according to Parker & Waud (1971). Maximal output for acid secretion was 130 μmols/min ±32.5 (s.e. mean) and for GMBF, 36 ± 8.1 ml/min. Mean Km ± s.e. mean for acid and GMBF are shown in Table 1.

Table 1

	Acid Secretion ED_{50}	*GMBF* ED_{50}
Histamine	19 ± 4.6	8.4 ± 2.7
Histamine and mepyramine	15 ± 6.6	9.7 ± 3.2
Histamine and cimetidine		
(2.5)	112 ± 9.8*	9.0 ± 4.1
(5.0)	208 ± 14.2*	22.6 ± 7.4
(10.0)	356 ± 22.9*	78.8 ± 12.7*

* $P < 0.05$ compared with histamine alone (analysis of variance applied to regression).

Mepyramine was without effect on either acid secretion or GMBF. All the doses of cimetidine produced parallel shifts of the log dose response curve as shown by the increasing Km and an unchanged V_{max} indicating competitive inhibition. Only the highest dose of cimetidine had a significant effect on GMBF and this was competitive antagonism. These results indicate that the gastric mucosal vasculature in the dog Heidenhain pouch is more sensitive to histamine than the parietal cell and less sensitive to cimetidine.

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References

GERKENS, J.F., FLEXNER, C., OATES, J.A. & SHAND, D.G. Prostaglandin and histamine involvement in the gastric vasodilator action of pentagastrin (1977). *J. Pharmac. exp. Ther.* **201**, 421–426.

HOLTON, P. (1973). Catecholamines and gastric acid secretion. In: *Pharmacology of the gastrointestinal tract and motility* **Volume 11** 39a pp. 287–315. Oxford Pergamon.

KNIGHT, S.E. & McISAAC, R.L. (1977). Neutral red clearance as an estimate of gastric mucosal blood flow in dogs. *J. Physiol. Lond.*, **267**, 45–46P.

PARKER, R.B. & WAUD, D.R. (1971). Pharmacological estimation of Drug-receptor dissociation constants. Statistical evaluation. 1. Agonists. *J. Pharmac. exp. Ther.* **177**, 1–12.