

Leading article

Histamine and the pathogenesis of duodenal ulcer disease

A key role for histamine in the physiological control of gastric acid secretion was established with the advent of the histamine H₂-receptor antagonists which have *in vivo* been shown to inhibit virtually all forms of basal and stimulated secretion.¹

These data can be seen to support the common mediator hypothesis championed in the last three decades by Code^{2,3} and which states that secretory stimulants such as gastrin and acetylcholine do not act directly on the parietal cell, but through mobilisation of histamine from endogenous stores. The histamine in turn acts on the histamine H₂-receptor.

The presence of histamine stores in the gastric mucosa has clearly been established, although the type of storage cell is species dependent, being predominantly the enterochromaffin-like cell in the rat⁴ but the mast cell in most other species including dog and man.⁵ The ability of secretory stimulants to release histamine from these stores by action on specific receptors is, however, unproven⁶ and is often inferred from changes in histamine content of gastric juice, or venous blood.

The possible presence of specific receptors for secretory stimulants on the parietal cell itself is still a matter of controversy, although a recent paper by Soll and coworkers⁷ indicates specific binding of iodinated gastrin 17 to canine parietal cells. Potentiating interactions between histamine and the other secretory stimulants at the parietal cell level have led to the hypothesis that histamine acts in a permissive role, markedly amplifying the effect of gastrin and acetylcholine on parietal cell receptors. It is the removal of this permissive effect of histamine, which accounts for the inhibitory actions of H₂-receptor antagonists.

Whatever the exact nature of the underlying mechanisms involved, the ability of histamine H₂-antagonists to inhibit gastric acid secretion has given them an important therapeutic role in duodenal ulcer disease. This reflects the fact that although the pathogenesis of duodenal ulcer is still not clear, inappropriate acidification of the duodenum is a fundamental factor.⁸

The question that now arises is: can the physiological role of histamine in stimulating acid secretion and the importance of acid secretion in the aetiology of duodenal ulcer be connected to provide a pathological role for histamine in the disease?

A series of papers published by the Marburg group during the past decade⁹⁻¹¹ and culminating in the paper by Thon *et al*¹² in this issue of *Gut* have addressed this question.

In the past all too frequently studies of the dynamics of mucosal histamine in animals and man have been bedevilled by assays of inadequate sensitivity and specificity and this has led to considerable

controversy over the interpretation of results. The development of the fluorimetric method by Lorenz and coworkers¹³ and the enzymatic isotopic assay by Schaff and Beaven¹⁴ has, however, provided methods which, when applied appropriately, produce reliable data. Equally important is the choice of suitable patients and the methods for obtaining mucosal samples and their processing for histamine determinations. In these respects Professor Lorenz's studies are carefully controlled.

Up to the publication of the present paper the group's major finding was that the histamine content of the gastric mucosa was approximately 30% lower in duodenal ulcer patients than in controls and that on ulcer healing the concentrations increased to be even greater than in control subjects. This interesting observation has been confirmed by other workers,¹⁵ although Peden *et al*¹⁶ suggested that the decreased mucosal histamine concentrations might be associated with cigarette smoking, rather than specifically with the ulcer disease.

This lower histamine content of the gastric mucosa could be the result of an increased metabolism, or the rate of histamine release exceeding the ability of the mucosa to replenish the stores with increased synthesis, or uptake. That the former reason is unlikely is indicated by the fact that the same group of workers have shown a parallel decrease in the activity of the major histamine metabolising enzyme, histamine methyl transferase in patients with duodenal ulcer.¹⁷

Data to support the alternative possibility (a secretagogue-driven depletion of mucosal stores, uncompensated by increased synthesis or uptake of histamine), is equivocal. Early studies in the rat indicating depletion of mucosal histamine after stimulation of acid secretion combined with the appearance of histamine in the gastric juice and in gastric venous blood, formed one of the cornerstones of the evidence supporting a physiological role for histamine.^{18 19} Recently Ruoff and coworkers have demonstrated histamine release from rat 'histaminocytes' in response to carbachol stimulation.²⁰ This may, however, relate to the peculiar storage characteristics in this species. In contrast, a recent study in the conscious dog²¹ provided no evidence for a lower histamine content of the gastric mucosa during pentagastrin stimulated acid secretion.

Failure to measure changes in the histamine content of the gastric juice may not necessarily argue against release of histamine from mucosal stores, because of the considerable capacity of the mucosa to metabolise histamine. For example, high concentrations of histamine methyl transferase have been detected in the parietal cell.²² Despite this, Lorenz and coworkers have shown that pentagastrin and insulin increased output of histamine in gastric juice of normal volunteers,²³ an effect confirmed for pentagastrin in subjects with duodenal ulcer.²⁴ For this increase in histamine output, paralleled by a reduction in mucosal content to be considered a causal factor in pathogenesis of duodenal ulcer it is assumed to be associated with an increased acid output.

Although basal acid secretion in normal subjects and patients with duodenal ulcer showed no relationship to mucosal histamine concentrations, there was a highly significant inverse relationship between individual peak acid output in response to pentagastrin and mucosal histamine concentrations. There was also a direct relationship between the decrease in acid output after vagotomy and the increased mucosal histamine

concentrations.²⁵ From these observations Lorenz derived a model relating histamine to the gastric hyperchlorhydria seen in duodenal ulcer disease. Patients with duodenal ulcer have an increased vagal drive leading to augmented histamine release and a decreased mucosal histamine. This combined with decreased histamine inactivation (lower concentrations of histamine methyl transferase), lead to gastric hypersecretion and consequent disease. Vagotomy abolished the vagal drive, decreased histamine release (and increased histamine content) which led to a reduction in stimulated gastric acid secretion.

A number of unresolved questions cast doubt on this model, however. The fact that vagotomy decreases histamine release has to be balanced against the observation that the operation simultaneously increases the concentration of the histamine metabolising enzyme which should lead to smaller mucosal stores. For a net increase in stored histamine to occur, the former process must outweigh the latter.

More importantly, it is difficult to reconcile the model with the fact that H₂ antagonists mimic the effects of vagotomy.¹⁵ Although vagotomy could lead to decreased release of histamine from mucosal stores, there is no evidence to support a similar role for H₂ antagonists, because they are assumed to act solely at the parietal cell level. Indeed, in a recently published paper²⁶ Man *et al* confirmed that cimetidine had no action in inhibiting histamine release into gastric juice or plasma caused by pentagastrin infusion in patients with duodenal ulcer. In addition, evidence from other types of histamine-storing cells suggests that H₂ antagonists could actually increase histamine release by inhibition of an H₂-receptor mediated negative feedback mechanism²⁷ and in the studies of Man *et al*, a transient rise in plasma histamine concentrations occurred after administration of cimetidine.²⁶

The findings reported in the paper in this issue of *Gut* that the mucosal histamine content in duodenal ulcer patients is lower in all areas of the stomach and duodenum than in control subjects (a situation reversed after vagotomy) also casts doubts on the model proposed earlier by Lorenz. It is possible that the changes observed in tissue histamine concentrations in duodenal ulcer patients are a consequence, rather than the primary cause, of the disease and Lorenz has put forward some interesting alternative hypotheses.

One attractive idea is that gastric hypersecretion in duodenal ulcer caused by either increased vagal drive, or hypergastrinaemia leads to an increased back diffusion of hydrogen ions in the stomach and the duodenum. This in turn could lead to histamine release and decreased histamine stores. Release of histamine from the gastric mucosa caused by acid back diffusion, particularly in the presence of bile salts or aspirin, has been documented.^{28, 29}

Part of the attraction of this hypothesis is that it can still be seen to support a pathological role for histamine, because the histamine released in the gastric mucosa could augment the stimulation of acid secretion, while that released in the duodenum could lower mucosal resistance by, for example, an effect on the vasculature. The hypothesis does however beg the question of why the histamine released in the gastric mucosa does not lead to damage in the stomach.

If the lower mucosal histamine content is a consequence of acid

hypersecretion, then H₂ antagonists might also be expected to increase the histamine content of not only the fundic mucosa, but also of other parts of the stomach and duodenum after healing of the ulcer. Unfortunately data are not available to answer this key question.

Another antisecretory drug, omeprazole has, however, been studied.³⁰ In duodenal ulcer treated for one month with omeprazole 82% inhibition of acid secretion was achieved, but this was not accompanied by a change in gastric mucosal histamine content. Although not stated,³⁰ it must be assumed that the ulcers healed on omeprazole therapy and if so the situation regarding histamine concentrations differ from that seen after vagotomy and H₂ antagonist therapy and calls into question the role of acid hypersecretion. Clearly further work is required.

An alternative hypothesis involving a role for gastrin is also suggested by Lorenz.¹² In the rat at least, gastrin has been shown to stimulate the activity of the histamine forming enzyme, histidine decarboxylase.³¹ Antisecretory drugs and vagotomy can lead to increased circulating gastrin concentrations as a consequence of the elevation of antral PH. In rats omeprazole has been shown³² not only to increase plasma gastrin, but also oxyntic mucosal histidine decarboxylase activity and mucosal histamine content. These effects are paralleled by an increase in the density of the enterochromaffin-like cells in the mucosa. The relevance of these findings to man is however unclear, as only relatively low concentrations of histidine decarboxylase are found in human mucosa¹¹ and storage of histamine is in mast cells rather than enterochromaffin-like cells. These differences may account for the failure of omeprazole to increase gastric mucosal histamine content in patients with duodenal ulcer.

The possible involvement of peptidergic neurones¹² in the control of histamine concentrations in the gastroduodenal mucosa is certainly a novel hypothesis which will require further animal and clinical studies.

In conclusion therefore, although the involvement of histamine in duodenal ulcer disease is established because of its central physiological role in the control of gastric acid secretion, it remains to be seen if this is only the consequence of other primary pathological factors. One fact is certain. Histamine will continue to stimulate gastroenterologists, but they may well suffer from histamine induced headache.

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