Short communications

Mobilization of gastric mucosal histamine and gastic secretion after H_2–receptor blockade

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The effects of two H_2-receptor antagonists (burimamide and metiamide) on the mobilization of gastric mucosal histamine, as shown by its urinary excretion and acid secretion following pentagastrin infusion, were studied in rats provided with Heidenhain pouches. Pentagastrin-induced secretion was completely inhibited without major alterations in urinary excretion of histamine. These observations can easily be reconciled with the hypothesis that pentagastrin is not a direct stimulant of the parietal cell.

Extensive work has been done to elucidate the mode of action of gastrin (for references see Kahlson, Rosengren & Svensson, 1973). Injection of gastrin evokes two well-known phenomena: mobilization of gastric mucosal histamine and hydrochloric acid secretion. It has been suggested that the mobilization of histamine (i.e. its release and new formation) is closely linked to the excitation of the parietal cells by gastrin. This concept finds support in the discovery of H_2-receptor antagonists, which competitively block the HCl-stimulatory effects of histamine and pentagastrin (Black, Duncan, Durant, Ganellin & Parsons, 1972; Black, personal communication). The object of the present study was to see whether these antagonists inhibit pentagastrin-induced secretion without interfering with mobilization of mucosal histamine.

Methods.—Female rats of the Sprague-Dawley strain were provided with Heidenhain pouches according to Alphin & Lin (1959). Before each experiment, the rats were fasted for 16 h and were allowed to drink water and Tyrode solution. During the actual experiment the rats were kept unanaesthetized in Bollman cages. Gastric juice was collected in 30 min samples by a perfusion technique (Svensson, 1970) and analysed for HCl by titration against 0·1 N NaOH, with phenol red as indicator. Pentagastrin (Peptavlon ICI 50123) and two H_2-receptor antagonists, burimamide (*N*-methyl-*N'* [4-(4(5)-imidazolyl)butyl] thiourea) and metiamide (*N*-methyl-*N'* [2[(5-methyl imidazol-4-yl)methyl thio] ethyl] thiourea), were infused via a polyethylene tube inserted in a tail vein. In all experiments, gastric juice and urine were collected simultaneously by a technique previously described (Johansson, Lundell, Rosengren & Svensson, 1972). The total amount of histamine excreted was assayed on the guinea-pig isolated ileum which had been treated with atropine.

During the actual experiment 0·9% w/v NaCl solution (saline) was infused for two 2 h periods, after which pentagastrin was added to the infusate. The H_2-receptor antagonists were infused for 1 h before administration of the stimulatory compound and the infusion continued for the rest of the experiment.

Results.—The effects of the H_2-receptor antagonists were studied in six Heidenhain pouch rats. Before the infusion of either burimamide or methiamide in a dose of 4×10^{-5} mol $kg^{-1}h^{-1}$, the interdigestive secretion was $2{\cdot}3\pm0{\cdot}70$ (S.E. of mean) μEq/30 minutes. Administration of pentagastrin in a dose of 1 μg/h, induced a rapid increase in acid secretion with a peak response of $91{\cdot}8\pm21{\cdot}74$ (S.E. of mean) μEq/30 min after 90 min, after which acid secretion slowly diminished. Burimamide significantly reduced the secretory $26{\cdot}4\pm10{\cdot}75$ (S.E. of mean) μEq/30 min periods studied, with a level of significance of at least $P<0{\cdot}05$. A peak response of $26{\cdot}4\pm10{\cdot}75$ (S.E. of mean) μEq/30 min was obtained after 90 min, after which secretion faded. Metiamide, on a molar basis, was more effective than burimamide in that it completely abolished acid secretion in response to pentagastrin. These results are summarized in Figure 1.

Gastrin infusion induces a substantial release of histamine from the gastric mucosa with simultaneous elevation of the rate of histamine formation, events which are paralleled by an increase in the urinary excretion of free histamine (Johansson *et al.*, 1972). In the present experiments the urinary excretion of histamine in the fasting state before administration of pentagastrin was $18{\cdot}6\pm1{\cdot}97$ (S.E. of mean) μg/2 hours. On infusion of pentagastrin, urinary excretion of histamine rose to

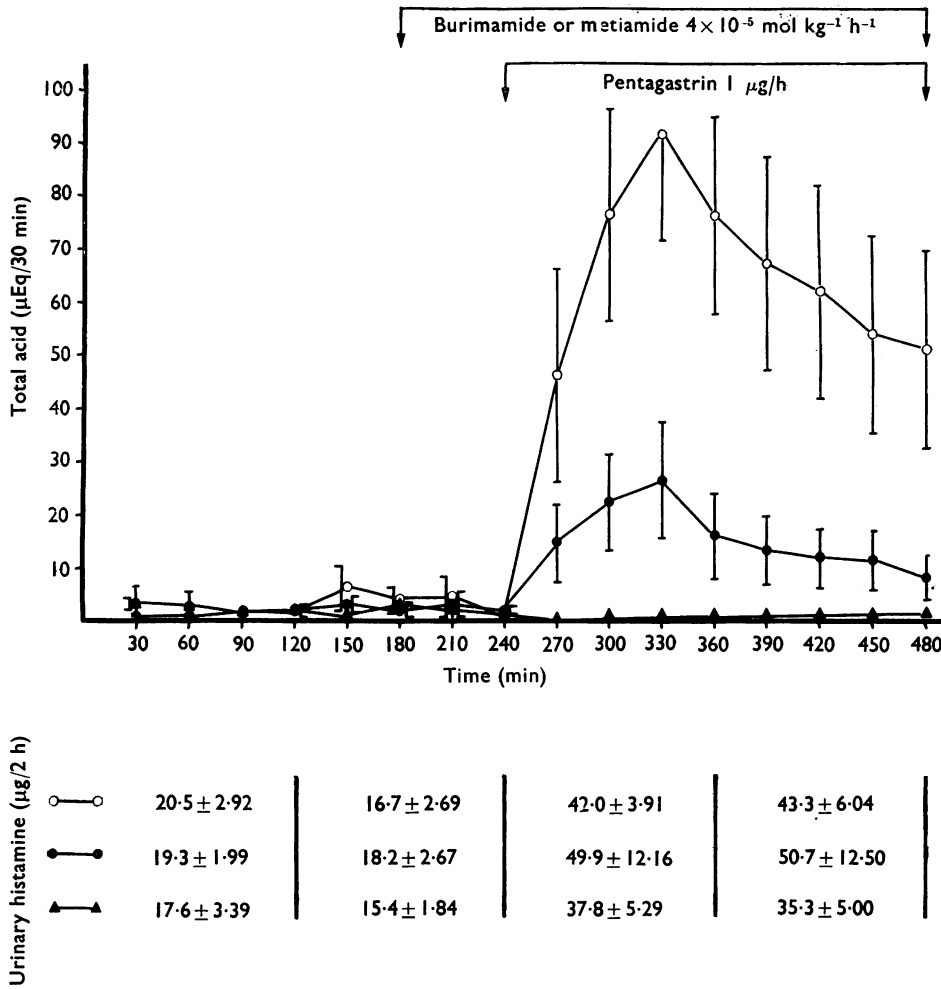

FIG. 1. Acid secretion and urinary excretion of histamine in six Heidenhain pouches in response to infusions of pentagastrin, 1 μg/h (○——○) and to pentagastrin in combination with either burimamide, 4×10^{-5} mol $kg^{-1}h^{-1}$ (●——●) or metiamide, 4×10^{-5} mol $kg^{-1}h^{-1}$ (▲——▲). Gastric juice and urine were collected simultaneously. Means±S.E. of the mean are given.

42·0±3·91 (S.E. of mean) μg/2 h; this rate was maintained for the next 2 h period. The combination of pentagastrin and burimamide was not accompanied by a significant difference in histamine excretion as seen in Figure 1. Metiamide, in a dose which completely blocked the secretory effect of pentagastrin, did not initially alter the amount of histamine mobilized since equal amounts of histamine were excreted as with pentagastrin infusion alone. The urinary histamine was, however, slightly less in the second 2 h period and differed significantly ($P<0.005$) from that obtained with pentagastrin alone.

Discussion.—Burimamide (Black *et al.*, 1972) and metiamide (Black, personal communication) have been characterized as effective blockers of histamine receptors on the parietal cells. In the present study, their inhibitory effects on pentagastrin-induced HCl-secretion have been confirmed. However, the increase in urinary excretion of histamine, due to release and new formation of gastric mucosal histamine, produced by pentagastrin infusion, is largely unaffected. These observations could thus easily be reconciled with the hypothesis that pentagastrin is not a direct stimulant of the parietal cell but depends on an

intermediary mechanism, namely the mobilization of histamine. In the present study, the changes in urinary histamine produced by pentagastrin infusion alone, and in combination with the H_2-receptor antagonists, have not been extended to determinations of histamine metabolism within the gastric mucosa. Such studies could further elucidate the small but significant reduction in urinary histamine, observed after a time, on combining metiamide with pentagastrin as compared with the effects of pentagastrin alone.

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