GASTRIC HISTAMINE RECEPTORS AND CYCLIC AMP

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INTRODUCTION

Histamine, a highly active biogenic amine continues to attract the attention of research workers despite recurring disillusion. It is a naturally occurring autacoid found in many tissues throughout the body and is concentrated in mast cells and basophilic granulocytes of the blood (24,92). The biological functions of this widely distributed amine are still obscure. Pharmacological effects of histamine have been reported to differ in different animal species. This poses a serious problem to any generalizations. The principal pharmacological actions of histamine were described in a series of papers by Dale et al from 1910-1919 (30,31). They reported that histamine or $\beta$-imidazoylethylamine as it was referred to before, produced shock like symptoms.

Histamine has been known to produce gastric acid secretion as discovered originally by Popielski (86). He reported that both histamine and suitable tissue extracts promoted gastric secretion. Evidence that histamine acts as a chemical mediator for gastric acid secretion was provided by Ivy and Farrel (55). They reported that histamine acts directly...
upon the autotransplanted fundic pouch. Davies and Roughton (32) showed that histamine stimulated isolated rat gastric mucosa in vitro. Code et al. (26) reported a relationship between the output of histamine in the gastric juice and the volume of hydrochloric acid secretion, when the gastric secretion was stimulated by meal. Alonso and Harris (2) reported the activation of gastric acid secretion from gastric mucosa due to gastrin and methylxanthines.

Nature of histamine receptors:

With the introduction of several histamine antagonists, it became apparent that not all of the known pharmacological actions of histamine are antagonized equally well by the classical antihistamines. This led to postulation of two kinds of receptors, with which histamine interacts (4). These putative receptors are now conventionally termed $H_1$ and $H_2$ receptors (11,36). The $H_1$-receptor antagonists antagonize histamine-induced vascular responses. The $H_2$-receptor blockers inhibit gastric acid secretion. Differentiation of the two receptor types can now also be made by using agonists which are relatively specific for each receptor. Compounds such as 2-methyl histamine, 2-(2-pyridyl) ethylamine and 2-(2-thiazolyl) ethylamine show a greater selectivity for $H_1$-receptors, while 4-methylhistamine and dimaprit (S-(3-(N,N-dimethylamino) propyl isothiourea) show a greater selectivity for $H_2$-receptors (7,8,44,109). Receptor affinity is highly sensitive to apparently minor changes in the structure of the agonist molecule and it has been suggested that there are differences in the topography of the two receptors (42,43,44). Recently synthesized compounds designated as histamine $H_2$-receptor antagonists have been introduced in the literature (12-18). The $H_1$-receptor antagonists possess aryle or heteraryl rings which need not have a structural relationship to the imidazole ring of histamine. The aryl groups confer considerable lipophilicity and probably act as hydrophobic binding groups. The $H_2$-receptor antagonists are hydrophilic molecules and bear a structural relationship to histamine in having an imidazole ring and possessing a polymethylene chain. The chain terminates in a polar nitrogen atom which is uncharged and would not mimic the stimulant action of histamine. These new compounds inhibit histamine-induced gastric acid secretion and two of them have been found effective in man (101, 117, 118). These compounds are burimamide, metiamide and cimetidine. The clinical trials with these compounds were started in 1972 in patients suffering from peptic ulcer.

Effect of histamine of gastric secretion:

Ungar et al. (103) had found some evidence for stimulation by histamine of the secretory activity in the cartilaginous fish. Hogben (54) has shown that histamine could stimulate acid secretion from isolated gastric mucosa of the dogfish. Among amphibians, several species of frogs have been subjected to repetitive studies on the effect of histamine on gastric secretion. Keeton et al. (61), demonstrated that histamine injected into dorsal
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Histamine receptors in gastric mucosa:

Histamine has been strongly suggested as a mediator of gastric acid secretion in all species studied, including man. The classical antihistamines of H1 type e.g. mepyramine, promethazine and tripelennamine showed no antagonistic action (65). The possibilities could be that the drugs are unable to reach the active sites, or there are more than one kind of histamine receptor. Such a finding was a poser for pharmacologists concerned with classification of drug actions. Till late in 1972, Black et al. (11) defined the other histamine receptors, namely the H2-type of histamine receptors. Experiments were carried out in anaesthetized rats, potential inhibitors were given by rapid intravenous injection during the plateau of gastric acid secretion produced by continuous intravenous infusion of histamine. Burimamide, the H2-receptor antagonist was shown to inhibit the histamine stimulated gastric secretion in the anaesthetized rats (11). There were three independent pieces of evidence which suggested a relationship between H2-receptor antagonism and the inhibition of histamine-stimulated gastric acid secretion.
of histamine stimulated gastric acid secretion as shown by Black and co-workers (12). The continuous acid secretion produced by direct, electrical stimulation of the peripheral ends of the cut vagi could not be blocked by burimamide. But burimamide could inhibit pentagastrin-stimulated gastric secretion. Evidence that secretory inhibition is due to blockade of H₂-receptors comes also from a comparison of the H₂-receptor antagonist potencies of several compounds measured in vitro, with their corresponding activities as inhibitors of gastric secretion, measured in vivo.

Gastric acid secretion and cyclic AMP:

Increasing evidence has shown that histamine enhances adenylate cyclase activity in many tissues (77,105,106,107,112). It is believed that cyclic adenosine 3', 5'-monophosphate (cyclic AMP) is directly responsible for the physiological effects of histamine (70,74,75,78,89,99,100,104,110,111,113).

It is well known that cyclic AMP is a "second messenger" in the action of many hormones and biogenic amines and is able to mimic their action on the target cells (72,73,76,108). Evidence has accumulated that cyclic AMP is a mediator in histamine-induced gastric acid secretion (64). Alonso and Harris (2), reported the activation of gastric acid secretion due to gastrin and methylxanthines. Perfusion of rat gastric mucosa with dibutyryl cyclic AMP caused acid secretion (97). Bersimbaev et al. (9) observed that pentagastrin or histamine produced an increase in adenylate cyclase activity in rat gastric mucosa. The studies of Perrier and Laster (84,85) showed that histamine and histamine analogues, betazole stimulated parietal mucosal adenylate cyclase and caused significant elevation of cyclic AMP. Karppanen et al. (58) and Karppanen and Westermann (59) reported that histamine caused an increase in gastric cyclic AMP in the guinea pig gastric mucosa. Levine and Washington (63) suggested that since stimulation of acid secretion was accompanied by an increased production of cyclic AMP in gastric juice, it appeared likely that cyclic AMP plays a mediating role in the human gastric secretory responses to histamine and betazole. Bieck et al. (10) using denervated pouches of the stomach fundus (Heidenhain Pouch dogs) reported that histamine produced a dose-dependent elevation of cyclic AMP and hydrochloric acid secretion. They further reported a causal relationship between cyclic AMP elevation and acid output. H₁-receptor blocking agent, diphenhydramine even in a concentration as high as 3.3 x 10⁻⁴M only slightly inhibited the histamine stimulated production of gastric acid (58,59). It is suggestive that the increased cyclic AMP levels, stimulate protein kinase to stimulate carbonic anhydrase activity and finally the H⁺ formed is secreted.

Histamine - H₂-receptors and adenylate cyclase - cyclic AMP:

H₂-receptor inhibitors, such as burimamide, metiamide and cimetidine, are highly active inhibitors of histamine induced gastric acid secretion (25). Recent studies of Main...
by Black and co-workers (12). Stimulation of the peripheral nervous system could inhibit gastric acid secretion, and burimamide could inhibit the etorvirenhibition is due to block-a-receptor antagonist potencies and binding activities as inhibitors of cyclic AMP activity. Furthermore, the acid secretion was inhibited by histamine H2-receptor antagonists burimamide, metiamide and cimetidine.

The selective H2-receptor agonist, 4-methylhistamine stimulated the gastric acid secretion which was inhibited by metiamide, the H2-receptor antagonist whereas the selective histamine H1-receptor agonist, 2-pyridylethylamine had no effect on acid output (67,68). It has been previously suggested by Verma and McNeill (105) that cardiac histamine H1-receptors are associated with the enzyme adenylate cyclase. McNeill and Verma (77) reported that histamine and its analogues, 3-(β-aminoethyl) 1,2,4 triazole and betazole all stimulated rat gastric adenylate cyclase in a dose-dependent manner. Burimamide antagonised the agonist responses. McNeill and Verma (77) further confirmed that H2-agonist, 4-methyl-histamine activated gastric adenylate cyclase and this action was inhibited by burimamide. Perrier and Laster (85) suggested the association of adenylate cyclase activity to the histamine sensitive guinea pig gastric mucosa. Sung et al. (98) have shown that rabbit gastric mucosa contains adenylate cyclase. They further reported that various histamine analogues activated the adenylate cyclase prepared from the gastric mucosa. It has been suggested that adenylate cyclase-cyclic AMP system may be involved in histamine gastric acid secretion (22).

It has been reported in the literature (23,33,41,60,62) that gastrin oligopeptide elevated cyclic AMP levels in the gastric mucosa of rats when administered with theophylline. But gastrin oligopeptide does not stimulate adenylate cyclase prepared from gastric mucosa of mammals; while histamine does so. It is thus suggestive that histamine interacts directly with adenylate cyclase of parietal cells. Dousa and Code (35), Bunce and Parsons (21) and Parsons (82) reported that specific H2-agonist can stimulate gastric acid secretion. The H2-receptor antagonist blocked the above responses (3).

Recently Parsons et al. (83) described Dimaprit, a highly specific H2-receptor agonist. It has 0.0001% of the activity of histamine H1-receptor. Dimaprit stimulated gastric acid secretion in rat, dog and cat in which it had, respectively approximately 19, 58 and 400-500% the activity of histamine. In the dog and cat the maximum secretory response to dimaprit was significantly greater than that obtained to histamine. Recent findings of Brown et al. (19) lend support to the hypothesis that histamine-induced gastric acid secretion in the rat involves H2-receptors.

Work by the authors (77,105,106,107,112) and by other investigators (10,37,45,56,71,93,95) provides strong evidence that H2-receptors in gastric mucosa of various species is associated with adenylate cyclase and the possibility that the H2-receptors may be an active site on the adenylate cyclase molecule (81). Scholes et al. (96) established the...
presence of a histamine H$_2$ sensitive adenylate cyclase system in dog gastric mucosa. They performed the experiments with mixed cell preparations containing 25-35% parietal cells. They concluded that H$_2$-receptor adenylate cyclase system may be located on the parietal cells.

Clinical evaluation of H$_2$-receptor antagonists:

The H$_2$-receptor antagonists, burimamide, metiamide, and cimetidine all have been reported to block the histamine-induced gastric acid secretion (6,49,50,66,80,90). Metiamide, first orally active H$_2$-receptor antagonist proved to be very effective in inhibiting the gastric acid secretion induced by variety of secretory stimulants and in preventing the development of gastric ulcers (19,20,29,115). Clinical trials with metiamide were carried out by Haggie et al. (46,47) and Henn et al. (53). They showed that metiamide could inhibit the acid and pepsin secretion in gastric secretion studies on patients suffering from peptic ulceration. Metiamide was administered intravenously in these patients. Metiamide caused marked symptomatic relief, and there was evidence that ulcer healing occurred during the treatment (80). H$_2$-receptor antagonists have shown therapeutic promise in the treatment of Zollinger-Ellison Syndrome (69). Richardson and Walsh (91) reported that metiamide (200-300 mg) inhibited acid secretion transiently (2½ hours) in all Zollinger-Ellison syndrome patients. The treatment of choice for the Zollinger-Ellison syndrome is total gastrectomy. It is suggestive that H$_2$-receptor antagonists may be a substitute for surgical therapy. However, metiamide can induce bone-marrow depression in man. This is thought to be due to the thiourea moiety present in metiamide molecule probably unrelated to H$_2$-receptor block itself (37,39,91).

REFERENCES

acid secretion (6.49.50,66.80,90). Rations containing 25-35% parietal cell mass may be located on the
metamidame, and cimetidine all have significant effects on gastric acid secretion (6.49.50,66.80,90). It has been shown that metiamide could improve the pyloric antrectomy in dogs and cimetidine in human patients. This suggests that the Zollinger-Ellison syndrome may be associated with metiamide treatment in these patients. Metamidame is effective in inhibiting acid secretion in all Zollinger-Ellison patients. Metiamide may have therapeutic promise in the treatment of Zollinger-Ellison syndrome. Metiamide is an orally active histamine H2-receptor antagonist. The pharmacology of metiamide and metimidine shows that metiamide is a new H2-receptor antagonist. Metiamide is effective in inhibiting acid secretion and mucosal ulcer healing in patients suffering from gastrin ulceration. Metiamide is an orally active histamine H2-receptor antagonist. The pharmacology of metiamide and metimidine shows that metiamide is a new H2-receptor antagonist.


