

HISTAMINE AND THE GASTROINTESTINAL TRACT

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Histamine occurs throughout the gastrointestinal tract, in enterochromaffin-like cells, restricted to the fundic mucosa of the stomach, mast cells and nerves. Histamine is actively produced and released in enterochromaffin-like (ECL) cells, rich in the synthesis enzyme, histidine decarboxylase (HDC), while it is mainly stored in mast cells.

Histamine exerts its effects through H₁, H₂, H₃ and H₄ receptors. Histamine H₁ receptors are reported to be expressed on enterocytes, connective tissue cells, muscle layer, blood vessels, immune cells and ganglion cells of the myenteric plexus in the human intestine¹. H₂ receptors appear to be located on parietal cells in the fundic mucosa² and they have also been found in the intestinal epithelium, immune cells and myenteric ganglia in humans¹. The presence of H₃ receptors in periphery remains controversial. H₃ receptor mRNA expression is reported to be undetectable in peripheral tissues of humans and rats^{3,4,5} or alternatively to be restricted to liver and epithelia, including the mucosa of the gastrointestinal tract⁶. Immunostaining of human intestinal tissues failed to reveal the presence of H₃ receptors¹. The ganglia of the enteric nervous system are negative for H₃ receptor mRNA expression¹. H₄ receptor mRNA appears to have a moderate to low expression in human stomach, small intestine and colon^{7,8}. Immunostaining revealed that enterocytes, intraepithelial neuroendocrine cells and leucocytes express the H₄ receptor in human intestinal tissue¹.

Histamine regulates multiple functions at the gastrointestinal level. Development of highly selective agonists and antagonists has been of great value in characterizing the different responses to histamine and the nature of the receptor involved^{9,10,11}. Contraction of intestinal smooth muscle is described as one of the best characterized responses mediated by H₁ receptors. Throughout the gastrointestinal tract, contractile effects are also exerted on vascular smooth muscle and on endothelial cells, this latter resulting in an

increase in vascular permeability. H₂ receptors, located on parietal cells, are potent stimulants of gastric acid secretion. It is largely recognized that the development of H₂-receptor antagonists revolutionised the treatment of peptic ulcer and of gastroesophageal reflux disease. The role of H₃ and H₄ receptors is less well defined. Prevention of acute gastric injury, stimulation of mucus production and increase in gastric epithelial cell proliferation in the rat appear to be regulated by H₃ receptors¹². The regulation of epithelial cell turnover could be of strategic importance in prevention and repair of gastric damage, suggesting a functional link between these H₃-receptor mediated effects. Proliferation is enhanced not only in the stomach but also in small intestine and colon, and the effect is selectively exerted on cells located in the proliferative compartments¹³. H₃ receptors also regulate neurotransmission in the myenteric plexus. Antagonists of H₄ receptor have been recently shown to reduce tissue damage and inflammation in a rat model of colitis, suggesting a role of the receptor in gut inflammation¹⁴.

Mutant animals, genetically lacking mast cells, HDC or a specific histamine receptor have been generated in an attempt to elucidate the role of histamine, mostly at the gastric level. Deletion of mast cells in mice caused a 50% decrease of gastric mucosal histamine, while intragastric pH, serum gastrin level and responsiveness of ECL cells to exogenous gastrin were not affected. Morphology of the gastric mucosa remained unaltered, indicating that mast cell-derived histamine is not critical in the maintenance of gastric mucosal architecture¹⁵. Genetic lack of HDC in mice causes an increase in basal gastric pH and in serum gastrin levels. Mice were unresponsive to exogenous gastrin but not to histamine, indicating that histamine is essential for gastrin effect on acid secretion. Time-related increases in DNA content and thickness of the gastric mucosa were present, caused by an increase in ECL and parietal cell number^{15,16}. Mice deficient in H₂ receptor were unresponsive to both exogenous histamine and gastrin. Elevated serum gastrin levels and hyperplasia of the fundic mucosa were also present¹⁷. In mice deficient in both gastrin and H₂ receptor¹⁸, response to gastric secretagogues was lost and atrophy of the oxyntic mucosa developed, leading to the conclusion that histamine and gastrin are mutually linked in the control of acid secretion while histamine and the H₂ receptor do not exert a trophic effect and do not mediate the trophic action of gastrin¹⁹. These studies have been restricted to stomach but it should be necessary to examine the other regions of

gastrointestinal tract to establish a possible role of histamine in the maintenance of epithelial homeostasis. Mice devoid of H₁ receptor as well as of H₃ and H₄ receptor have also been generated, but possible modifications of gastrointestinal functions and morphology have not been investigated thus far.

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