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Role of histamine H_4 receptors in the gastrointestinal tract

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1. ABSTRACT

The location and functional role of histamine H_4 receptors (H_4Rs) in the gastrointestinal tract (GI) is reviewed, with particular reference to their involvement in the regulation of gastric acid secretion, gastric mucosal defense, intestinal motility and secretion, visceral sensitivity, inflammation, immunity and carcinogenesis. H_4Rs have been detected in different cell types of the gut, including immune cells, paracrine cells, endocrine cells and neurons; moreover, H_4R expression was reported in human colorectal cancer specimens. Functional studies with selective H_4R ligands demonstrated protective effects in several experimental models of gastric mucosal damage and intestinal inflammation, suggesting a potential therapeutic role of drugs targeting this new receptor subtype in GI disorders, such as allergic enteropathy, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and cancer.

2. INTRODUCTION

Histamine is a pleiotropic biogenic amine with a broad range of activities in both physiological and pathological conditions. Both histamine producing cells and receptors are extensively distributed within the body, suggesting that this amine is an important regulator of a wide variety of functions. Despite the intestinal effects of histamine were firstly described one century ago in the landmark paper by Dale and Laidlaw (1), research mainly focused on immunological and inflammatory effects of this amine, leading to the discovery of the histamine H_1 receptor (H_1R) antagonists, as the first anti-allergic drugs (2). In 1972, thanks to the pioneering work of Sir James Black and coworkers, the central role of histamine in the regulation of parietal cell acid secretion was clearly defined and histamine H_2 receptor (H_2R) antagonists became the standard therapy of gastric acid related diseases (3-5). Since then, two further receptor subtypes have been

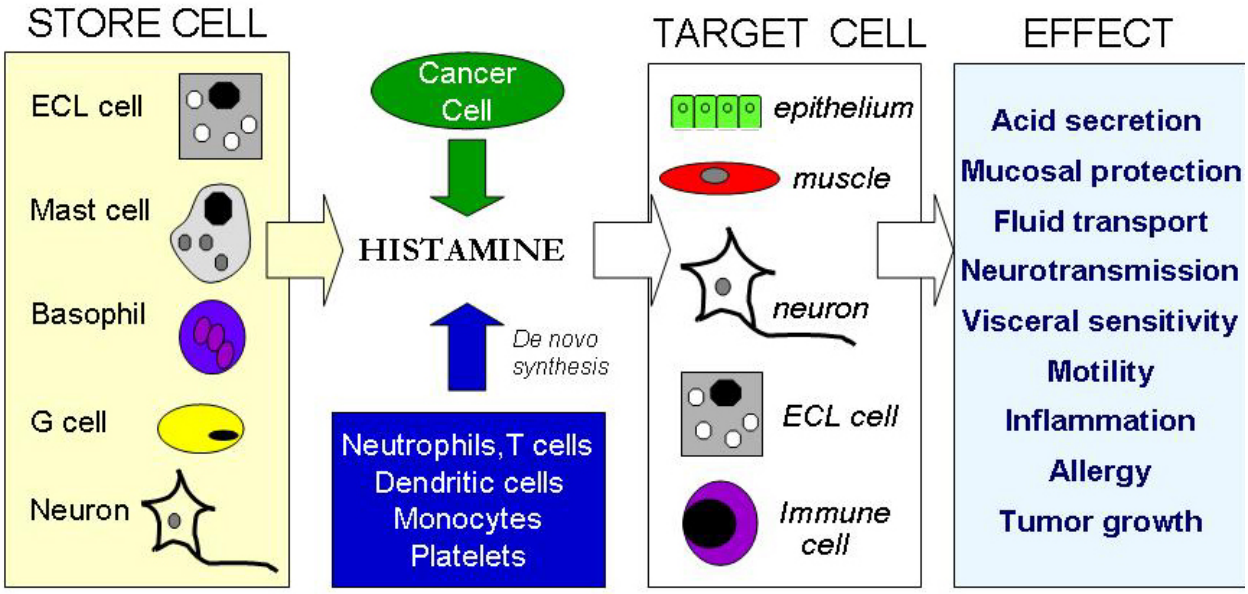

Figure 1. Scheme illustrating the producing and target cells of histamine, together with the main biological effects of histamine in the gastrointestinal tract. Histamine can be released from granules of store cells or produced by "*de novo synthesis*" in immune cells. Moreover, histamine can be produced and released from cancer cells and regulates tumor growth. ECL: enterochromaffin-like.

discovered, namely H_3 and H_4, and the research on histamine gained considerable interest again (6-12). Therapeutic fields have emerged for H_3 receptor (H_3R) ligands, with selective antagonists representing new drugs for cognitive, sleep and memory disorders (13, 14) and for obesity (15); on the other hand, based on the predominant location of H_4 receptors (H_4Rs) in immune and inflammatory cells, selective antagonists of this receptor are currently the object of intensive research, as potential candidates in the therapy of allergy, inflammatory disorders, neurophatic pain and pruritus (16-21). A large body of evidence has unraveled the occurrence of H_4Rs in the gastrointestinal (GI) tract, together with protective effects mediated by H_4R ligands in experimental models of GI damage, thus suggesting that this novel receptor subtype might represent a potential drug target in the treatment of functional GI diseases.

In the present review we report the available data concerning the location and functional role of histamine H_4Rs in the GI tract and the potential clinical implications for human diseases.

3. HISTAMINE IN THE GI TRACT: CELLULAR SOURCES, TARGETS AND RECEPTORS

In the GI tract, histamine is synthesized by histidine decarboxylase (HDC) enzyme and stored in various cell types, including mast cells, basophils, and enterochromaffin-like (ECL) cells; few reports suggest the occurrence of histamine in G cells and enteric neurons (Figure 1) (22-26). In addition, several myeloid and lymphoid cell types (dendritic cells, neutrophils, monocytes/macrophages, T cells and platelets), which do not store histamine, show high HDC activity and are capable of producing histamine to a varying degree, following activation by allergens, mitogens or cytokines (27-30). Finally, most malignant cells contain high concentrations of histamine that can regulate tumour growth via a paracrine or autocrine pathway (Figure 1) (31). Histamine stores greatly vary among species: in dogs and humans, mast cells account for the major histamine content; they are predominantly located in the mucosal surfaces of the whole GI tract and are mainly involved in IgE-mediated hypersensitivity in response to allergens and in reactions against parasites (32). In rodents, ECL cells are recognized as the major histamine-producing cells in the gastric mucosa, thereby representing a central regulatory pathway for the secretion of acid *via* the parietal cell (33, 34). Elevated concentrations of histamine have been shown in various inflammatory and neoplastic diseases, such as Crohn's disease, ulcerative colitis, irritable bowel syndrome (IBS), allergic enteropathy and colorectal cancer (32, 35-38).

In the GI tract, histamine plays a role in a number of processes, including acid secretion, mucosal defense, fluid transport, neurotransmission, inflammation, immunity and carcinogenesis, targeting a variety of cell types (Figure 1) (28, 31, 32, 39-42). These different biological functions involve the four known histamine receptor subtypes, identified to date, H_1, H_2, H_3 and H_4, which are differently expressed along the gut. Histamine H_1Rs mediate vasodilatation and increase in vascular permeability, smooth muscle contraction, intestinal fluid transport and visceral sensitivity; H_2Rs are mainly responsible for the physiological regulation of acid secretion from parietal cells, but also influence intestinal

Table 1. Histamine H_4R expression in the GI tract.

Species	Technique	Expression	References
Human	RT-PCR	Stomach	9
	RT-PCR	Small intestine	7-10, 47
	RT-PCR	Colon	8, 49, 53
	RT-PCR, Western blot analysis, Immunohistochemistry	Whole intestine	51
	RT-PCR	Colorectal cancer specimens	49, 53
	Western blot analysis, immunohistochemistry	Colorectal cancer specimens	53
Monkey	RT-PCR	Colon	50
Dog	RT-PCR	Small intestine	54
Pig	RT-PCR	Colon	48
Guinea pig	Immunofluorescence	Esophagus	57
Rat	Immunohistochemistry	Stomach (ghrelin-producing cells)	52, 55
	Immunohistochemistry	Whole intestine (myenteric plexus)	52
Mouse	RT-PCR	Peritoneal exudate	58
	RT-PCR	Small intestine (intra-epithelial lymphocytes)	59
	RT-PCR	Distal colon	56

RT-PCR: Reverse transcription-polymerase chain reaction

secretion, neurotransmission and immune responses; H_3Rs are primarily involved in gastric mucosal defense, inhibition of enteric neurotransmission and feedback regulation of histamine release (32, 43-46). Preliminary functional studies in transfected cells and *in vivo* experimental models seem to suggest the participation of H_4Rs in the GI effects of histamine. The H_4R has been shown to mediate a number of proinflammatory effects, including neutrophil, mast cell and eosinophil chemotaxis and release of inflammatory cytokines, thus representing a novel target in inflammatory GI diseases (17).

4. EXPRESSION OF H_4Rs IN THE GI TRACT

In the last decade, the occurrence of H_4Rs in the GI tract of different species, including humans, was demonstrated by the use of several techniques, such as quantitative reverse transcription-polymerase chain reaction (qRT-PCR), Western blot analysis and immunostaining (summarized in Table 1) (7-12, 47-59). Under physiological conditions, H_4R expression is rather low, as compared with bone marrow, spleen or liver, but it may be regulated by inflammatory stimuli. A recent study demonstrated a significant increase in H_4R density after treatment of mice with trinitrobenzenesulphonic acid (TNBS), a widely used model of inflammation, which reproduces human Crohn's disease (56, 60). More recently, it was reported that H_4R expression increases in the colon of mice genetically deficient of the Gi protein alpha2 subunit and the increase in receptor density parallel the colitis progression (61). The presence of H_4Rs was demonstrated in the human normal intestine and their distribution pattern was described in detail by histological analysis (49, 51, 53); H_4R staining was detected in leukocytes inside the small mucosal and submucosal vessels, neuroendocrine cells and, finally, in enterocytes at the apical end of the crypts of Lieberkun (51). The same study reported an increased expression of both H_1Rs and H_2Rs in patients with IBS or food allergies, with no change in H_4R mRNA levels (51). By contrast, H_4R expression was found to be reduced in colorectal cancer specimens, as compared to normal colonic tissue (49, 53).

5. HISTAMINE H_4R SELECTIVE LIGANDS

Since the cloning of the H_4R, a variety of ligands have been identified in search of selective tools to unravel H_4R-mediated tissue functions and of potential drug candidates (18-20, 62). In accordance with the high homology between H_4R and H_3R, most of the first-generation H_3R ligands (like imetit, immepip, thioperamide and clobenpropit) are now known to bind to the H_4R (16). The first highly selective histamine H_4R antagonist, namely JNJ7777120, was developed by Johnson and Johnson Pharmaceuticals and it became the reference antagonist for pharmacological investigation, displaying more than a thousand fold selectivity over other receptor subtypes (19, 63, 64). Other H_4R antagonists were developed by academic research groups and by several pharmaceutical companies (58, 62, 65, 66). Histamine H_4R agonists were also described, such as 4-methylhistamine and VUF8430; these compounds, however, still retain affinity for the other histamine receptor subtypes (67, 68). To complicate matters, the selectivity profile of most H_4R ligands was found to greatly vary according to the species; in addition, some ligands were found to behave as "protean" ligands, displaying antagonism, partial, total or inverse agonism activity, depending on the experimental assay (69,70). This hampers a clear understanding of H_4R pharmacology; in line with this, some studies were unable to ascribe the observed effects to agonism or antagonism at H_4Rs (71, 72). To support this, a recent study in rats reported that ischemia/reperfusion liver injury was reduced by H_4R stimulation and not blockade, as expected from the supposed inflammatory activity mediated by H_4Rs (73).

6. EFFECTS OF H_4R LIGANDS IN THE GI TRACT

Several studies have reported functional effects of H_4R ligands in both *in vitro* assays and in intact animals. Most data were obtained in rodents by the use of the reference H_4R antagonist JNJ7777120 (Tables 2 and 3).

6.1. Gastric acid secretion

The major role of histamine and of H_2Rs in the stomach is the regulation of acid secretion by the parietal

Table 2. Functional *in vitro* studies from the literature with H_4R ligands

Species	Experimental assay	Ligand	Effect	References
Human	Submucous plexus from surgical samples of small and large bowel	4-methylhistamine + JNJ7777120	Neuronal excitation	98
	Myenteric plexus from colon surgical specimens	JNJ7777120 VUF8430	No effect on electrically-evoked contractions	C. Pozzoli, unpublished
	COX-2-expressing colon cancer cells	Histamine + JNJ7777120	Proliferation and angiogenesis	49
Guinea pig (sensitized)	Esophagus (antigen challenge)	Thioperamide	Inhibition of mast cell chemotaxis and eosinophil infiltration	57
Rat	Duodenum	VUF8430 VUF10148 VUF10214	No effect on electrically-evoked contractions	95

COX-2: Cyclooxygenase-2

cell, as demonstrated in humans by the clinical efficacy of H_2R antagonists in various clinical settings (4, 5). Whereas gastric H_1Rs are mainly involved in the vasodilation and reactive hyperemia in response to acid challenge (39, 45, 74, 75), the role of H_3Rs is unclear. H_3Rs were detected in various cell types of the gastric mucosa, including ECL cells, cholinergic neurons and somatostatin D cells (39, 40, 43, 55); however, functional data were dependent on the species and the experimental assay (40, 44, 46). The negative regulation of histamine release from ECL cells has been proposed by several authors as the main function mediated by H_3Rs in the rat stomach (33, 43).

Early studies have reported a low H_4R expression in the human and rat stomach (Table 1); recently, more detailed information about the cell distribution of H_4Rs in the rat gastric mucosa was obtained by immunohistochemistry (55). In particular, as opposed to H_3Rs, H_4Rs do not occur in ECL cells and seem to be selectively located in endocrine cells (A-like cells) of the fundic mucosa producing the orexigenic peptide ghrelin (55). Functional experiments obtained in our lab in the anaesthetised rats with lumen-perfused stomach showed that the selective H_4R antagonist JNJ7777120 and its benzimidazole derivative VUF6002 (76) did not modify basal acid secretion or the hypersecretion induced by histamine; in addition, only JNJ7777120 reduced the acid secretion induced by pentagastrin (M. Adami, unpublished observations). The hypothesis of gastric secretory effects induced by H_4R activation, was not confirmed by the use of the H_4R agonist VUF8430, since the increase in acid secretion induced by this compound was fully prevented by the H_2R antagonist ranitidine and not by JNJ7777120 (77). In conclusion, the relevance of histamine H_4Rs in parietal cell function is still to be elucidated.

6.2. Gastric mucosal defense

As opposed to the key role played by histamine in the regulation of parietal cell function, its role in gastric mucosal defense has long been debated, since H_1R or H_2R selective ligands displayed either ulcerogenic or protective effects (44). The discovery of histamine H_3Rs and the use of (R)-alpha-methylhistamine and thioperamide have highlighted the protective effect of histamine in the gastric mucosa, since H_3R activation prevented the acute mucosal damage induced in rats by absolute ethanol, non-steroidal anti-inflammatory drugs, ammonia, concentrated HCl or stress (78-83). The protective effect was related to increase in mucus production, gastric mucosal blood flow, epithelial cell proliferation and activation of sensory nerves (83-85).

Data from our group have suggested a possible involvement of H_4Rs in histamine-mediated effects on mucosal defense (86); HCl-induced gastric lesions were not reduced by immepip and imetit, two formerly described as highly selective H_3R agonists, which are now known to display considerable affinity at histamine H_4Rs (16, 67). Indeed, subsequent data from our lab obtained with the selective H_4R antagonist JNJ7777120, would indicate that H_4Rs are involved in the ulcerogenic effects of histamine (71, 87). This compound was found to protect the rat and mouse gastric mucosa from the damaging effect of non steroidal anti-inflammatory agents and the mast cell degranulator compound 48/80 (Table 3). However, preliminary experiments from our group showed that in rats, but not in mice, the selective H_4R agonist VUF8430 significantly reduced indomethacin-induced lesions (Figure 2, Table 3) (71). From the available data, it is difficult to make a clear picture of the functional role of H_4Rs in the rat gastric mucosa, due to the similar behaviour displayed by H_4R agonists and antagonists. The occurrence of H_4Rs in endocrine cells of the rat fundus producing ghrelin (55, 88) could lead to speculate a possible role of histamine in the secretion of this peptide (Figure 3). In line with this, a link between histamine and ghrelin was indicated by recent data from our group, showing that ghrelin-induced gastroprotection is prevented by both H_3R and H_4R antagonists (89).

6.3. Intestinal motility and secretion

The intestinal effects of histamine were among the first effects of histamine described by Dale and Laidlaw (1). Nevertheless, most attention was devoted to the functional activity of histamine in the stomach and the effects on the bowel were disregarded. In the recent years, it has become apparent that intestinal mast cell mediators and enteric nervous system are key players in the intricate neuroimmune network, that regulates intestinal homeostasis and the inflammatory response to noxious stimuli (90). Histamine can influence neurotransmission at both submucous and myenteric plexus, thereby modifying intestinal secretion and motility, through the activation of the three receptors H_1, H_2 and H_3 (32, 39, 45, 46, 91-93). The occurrence of a new receptor subtype in the intestine was firstly hypothesized by Schworer *et al* (94), who identified in the porcine small intestine an H_3-like receptor

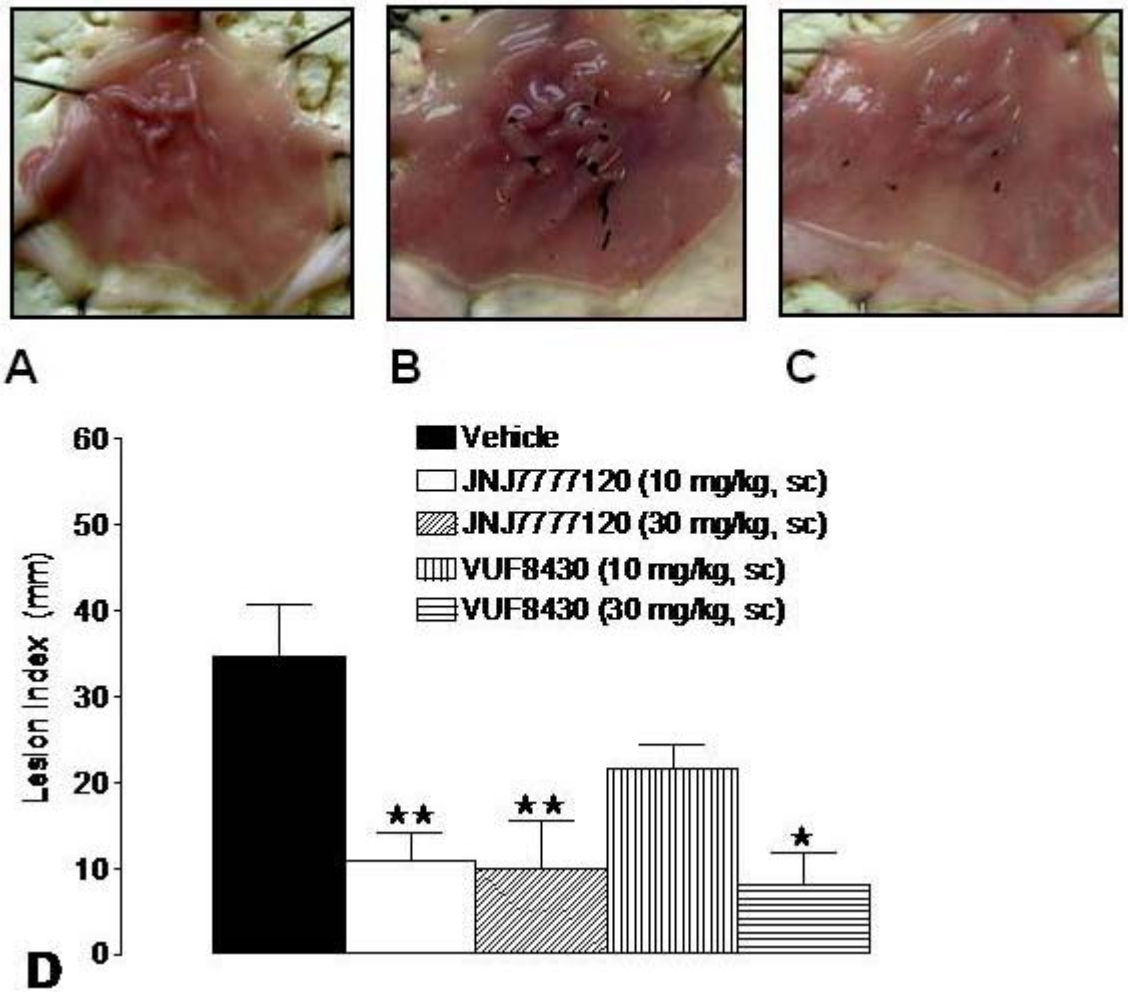

Figure 2. Effect of H_4R ligands on indomethacin–induced gastric damage in rats. *Upper panel*: macroscopic aspects of gastric mucosa from rats treated with subcutaneous (sc) injections of vehicle (A) or indomethacin (20 mg/kg), in the absence (B) or in the presence (C) of JNJ7777120 (10 mg/kg, sc). *Lower panel*: effects of indomethacin in the presence of vehicle or H_4R ligands (D). On the ordinate, macroscopic damage reported as *lesion index* in mm. Differences among multiple groups were made by using one-way analysis of variance (ANOVA), followed by Dunnett's test: *$p < 0.05$ and **$p < 0.01$ compared to the vehicle-treated group. Mean values ± SEM from 6-8 rats.

that was pharmacologically distinct from the proposed H_{3a} and H_{3b} receptors. These findings were subsequently confirmed by Oda *et al* (8), who characterized a new histamine receptor (called GPRv53) expressed in the small intestine, and afterwards by several independent groups (Table 1) (7-12).

Despite the presence of H_4Rs in the rodent myenteric plexus (52), the role of this receptor in the regulation of intestinal motility is apparently absent. In our lab, we were unable to detect any effect of either agonists or antagonists of H_4Rs on cholinergic neurotransmission in the isolated rat duodenum (95). Likewise, histamine H_4R ligands did not modify spontaneous or electrically-evoked motility in surgical specimens from human colon, suggesting that this receptor subtype does not play a role in the regulation of intestinal muscle contractility in humans (Table 2).

The stimulatory effects of histamine on intestinal transport were widely demonstrated in guinea pigs and humans (32, 92, 93, 96, 97). However, the receptor involved seems to differ across species: in the guinea pig, histamine increases intestinal ion and water secretion in both small and large intestine, *via* activation of H_2Rs located on epithelial cells and on colonic submucous plexus (96). In addition, prejunctional H_3Rs negatively modulate cholinergically-mediated intestinal secretion by removing the inhibitory control exerted by the adrenergic system (96). As opposed to animal findings, in the human intestine, histamine-induced increase in chloride secretion by colonic epithelium was exclusively related to activation of H_1Rs (92). A recent study in human submucous plexus from surgical specimens suggests, however, that histamine may induce excitation of enteric neurons through activation of all four histamine receptors (H_1R-H_4R) (98). The H_3R-

Table 3. Functional *in vivo* studies with H_4R ligands

Species	Experimental assay	Ligand	Effect	References
Rat	Indomethacin-induced gastric damage	JNJ7777120 VUF6002 VUF8430	Gastroprotection	71
	Compound 48/80	JNJ7777120	Gastroprotection	M. Adami, unpublished
	0.6N HCl-induced gastric damage	JNJ7777120 VUF6002	No effect	71
	TNBS-induced colitis	JNJ7777120 JNJ10191584	Inhibition of macroscopic and histological damage, neutrophil infiltration, TNFalpha and IL-6	116, 117
	TNBS-induced colitis	Thioperamide	Inhibition of macroscopic damage, neutrophil infiltration and TNFalpha	118
Mouse	Indomethacin-induced gastric damage	JNJ7777120	Gastroprotection	71
		VUF8430	No effect	71
	Cold/restraint stress	JNJ7777120	No effect	M. Adami, unpublished
	Ischemia/reperfusion-induced intestinal damage	Thioperamide	Inhibition of neutrophil infiltration	121
	Zymosan-induced peritonitis	JNJ7777120	Inhibition of neutrophil infiltration	64
		JNJ7777120 A-940894	Inhibition of neutrophil infiltration, PGD_2 and PGE_2	58, 111[1]
	Thioglycollate-induced peritonitis	JNJ7777120	No effect	64

TNBS: Trinitrobenzene sulphonic acid; [1]JNJ7777120 inactive in mast cell-deficient mice

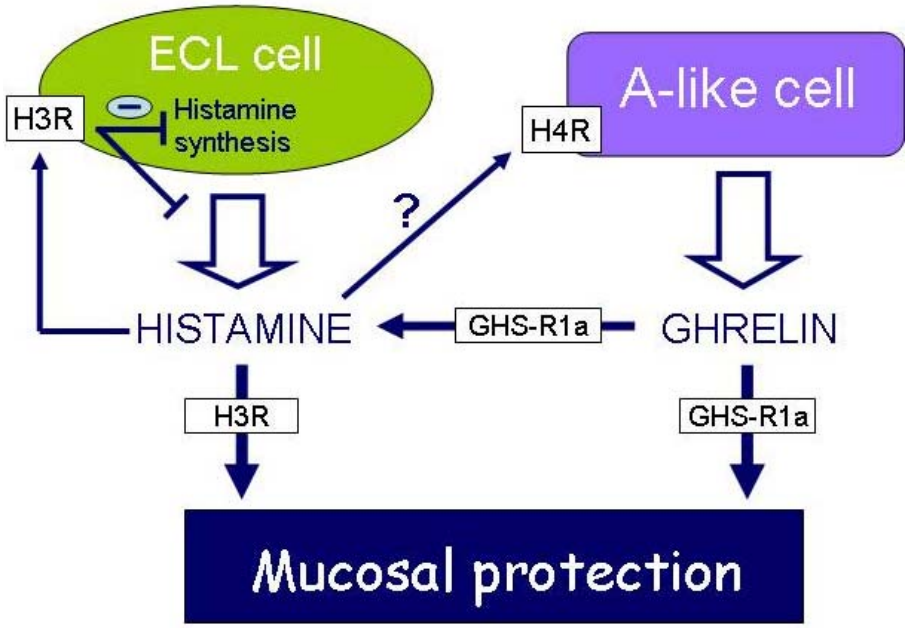

Figure 3. Scheme illustrating a proposed interaction between histamine and ghrelin in the rat gastric mucosa. Histamine and ghrelin are stored by ECL cells and A-like cells, respectively. Histamine release from ECl cells is under the negative regulation operated by the histamine H_3 receptor (H_3R); no functional role has been so far evidenced for the histamine H_4 receptor (H_4R) occurring in A-like cells. In the rat gastric mucosa the effects of ghrelin on mucosal protection are mediated by both the growth hormone secretagogue receptor type 1a (GHS-R1a) and the H_3R, suggesting the involvement of histamine in ghrelin-induced protection.

mediated excitatory effects on secretory neurons reported in this study are unexpected, in view of data from the literature showing lack of H_3R expression in the human bowel or of H_3R-mediated effects on intestinal contractility (51, 99). The pathophysiological significance of the excitatory action of histamine on secretory neurons is uncertain; hyperactivity of these neurons leads to neurogenic secretory diarrhoea, as observed in various pathological conditions, such as ulcerative colitis, Crohn's disease, allergic enteropathy or parasitic infection (90). In this connection, mast cells in colonic mucosal biopsies from IBS patients with diarrhoea release more histamine than in normal subjects (37); thus, it can be speculated that H_4R antagonists may be of therapeutic value in these GI disorders, as observed for mast cell stabilizers or H_2R antagonists (100, 101).

6.4. Visceral sensitivity

Visceral hypersensitivity is widely accepted as a mechanism that can explain many clinical symptoms associated with organic and functional bowel diseases (90, 102). Histamine, as other inflammatory mediators, has an important role in GI hypersensitivity reactions; once released from mast cells, it can easily reach the afferent sensory nerves nearby and activate neuron discharge, thus increasing visceral sensitization to painful stimuli (103). In line with this, treatment with mast cell stabilizers prevents lowering of pain threshold, which occurs during mucosal inflammation (90). According to the species, H_1R, H_2R or H_3R subtypes have been involved in the alteration of visceral pain perception induced by histamine (104-107). As opposed to the early studies, it is now clear that H_4Rs are expressed and are functionally active on neurons of the mammalian central and peripheral nervous system (52, 98, 108-110). To the best of our knowledge, no study has examined to date whether H_4Rs are located on afferent fibers of the enteric nervous system; in view of the inhibitory effects of H_4R antagonists in different pain models, it might be of interest to explore the effects of H_4R ligands in models of visceral pain (65, 111-113).

6.5. Inflammation and immunity

Accumulating evidence has suggested that histamine plays a key role in inflammation, immediate hypersensitivity reaction and cellular and humoral immune response (28, 30, 41). Preformed or *neosynthesized* histamine is produced during inflammatory response in several GI disorders, such as food allergy, IBD and IBS, and exerts multiple regulatory effects through the activation of both H_1Rs and H_2Rs (32, 37, 41, 114-116). However, the efficacy of medical therapy based on the use of antihistamines or mast cell stabilizers is unproven (115). The recent discovery of H_4Rs, mainly located in immune and inflammatory cells has further strengthened the role of histamine at this level. Given the ability of H_4Rs to modulate the function of mast cells, T cells, dendritic cells and eosinophils, it is natural to foresee a therapeutic potential of H_4R antagonists in inflammatory disorders of the GI tract. Indeed, both *in vitro* and *in vivo* studies provided evidence for a beneficial effect of H_4R antagonists as anti-inflammatory agents (Tables 2 and 3). Histamine H_4R antagonists were effective against the intestinal damage induced in rats by TNBS, a hapten which induces in rodents many of the macroscopic, histological and immunological hallmarks of the human IBD (60). In this assay, oral administration of JNJ7777120 produced a significant inhibition of macroscopic damage, neutrophil infiltration and the increase in TNFalpha and IL-6, two cytokines that play a critical role in the pathogenesis of the human disease (117-120). Other studies have confirmed the inhibitory effects of H_4R antagonists on neutrophil influx into peritoneal cavity or into the pleural cavity (65, 121). JNJ7777120 was partially effective in reducing zymosan-induced peritonitis, a model of acute inflammation which is reported to be mast cell-dependent, since the neutrophil influx induced by zymosan is reduced in mast cell-deficient mice (64, 122). The observation that the H_4R antagonist was ineffective in the peritonitis induced by thioglycollate (a mast cell-independent model) is consistent with the hypothesis than JNJ7777120 is acting on mast cells (64, 122). In line with this, analysis of peritoneal cell exudate in mice unraveled an expression of H_4R mRNA higher in naive animals, as compared to genetically modified mice, devoid of mast cells, suggesting that resident mast cells may be the predominant H_4R-expressing cell in the peritoneum (113).

Finally, the involvement of H_4Rs in the ischemia/reperfusion-induced damage was recently reported in mice (123); this findings, however, were obtained with the H_3/H_4 receptor blocker thioperamide, thus the evidence for a specific involvement of H_4Rs is lacking; in line with this, previous data obtained in rats showed that the effect of histamine on intestinal ischemia was related to activation of H_1Rs (124).

6.6. Carcinogenesis

The stimulatory effect of histamine on tumor growth has been known for long time (31). High levels of HDC activity and high concentrations of histamine have been detected in both experimental and human tumours, such as breast cancer, melanoma, small cell lung carcinoma, endometrial cancer and colorectal carcinoma (38, 49, 125-129). In addition, histamine content was correlated with the presence of lymph node and/or distant metastasis in colorectal cancer (49). Histamine was reported to act also as an angiogenic factor and induce vascular endothelial growth factor (VEGF) production, thus influencing the process of tumour invasion and metastasis (130, 131). The tumour promoting effects of histamine appear to be predominantly mediated by H_2Rs; in line with this, some encouraging results of clinical trials have shown increased survival of gastric and colon cancer patients after treatment with the H_2R antagonists cimetidine and ranitidine (132-134).

The recent discovery that histamine H_4R expression was detected in colorectal specimens has renewed the interest for the role of histamine in carcinogenesis and opened new horizons in this field. A recent study investigated the distribution of the different histamine receptor subtypes in the colorectal tumours compared to the normal mucosa, by different techniques such as RT-PCR, Western blot analysis and immunostaining (98). The study demonstrated the presence of H_1R, H_2R and H_4R expression in adenoma and human colon carcinoma at protein level; in addition, in line with previous studies ruled out the presence of H_3Rs in the human intestinal tissue (49, 51, 99). Histamine receptor expression pattern in neoplastic tissue was altered as compared to normal colonic mucosa, with significantly reduced expression of both H_1Rs and H_4Rs in tumour (98); this could favour H_2R-mediated regulation of tumour cell growth. Further studies are required to clarify whether H_4R downregulation has relevance in tumour progression and whether agonism at H_4Rs combined to H_2R antagonism would shift the process in the direction of tumour inhibition. It is of interest that H_4R activation reduced cell proliferation in a pancreatic carcinoma cell line and in human hematopoietic progenitor cell (135, 136). Recently, however, it was reported that the H_4R antagonist

JNJ7777120 and the H_2R antagonist zolantidine prevented the effects of histamine on cell proliferation, VEGF production and cyclooxygenase-2 (COX-2) induction in several colon cancer cell lines, without affecting basal cell proliferation (49). Collectively, these findings suggest that further studies are needed to assess the role of H_4Rs on tumor cell growth.

7. SUMMARY AND PERSPECTIVE

Over the past few years research on histamine H_4Rs has provided significant evidence for a role of this new receptor in a variety of histamine functions, emphasizing the concept that there is still much to learn about histamine and its versatile biology. The findings reviewed here strongly suggest that histamine H4Rs may participate in the GI effects of histamine; H_4R expression was found in different cell types and can vary under pathological conditions characterized by inflammation and malignancies. The beneficial effects demonstrated by H_4R antagonists in several models of GI mucosal damage, would lead to conclude that the H_4R could be a potential target candidate in the therapy of functional GI diseases. However, further studies with more selective ligands are needed to characterize the GI H_4R under both physiological and pathological conditions. This would be of utmost importance, when considering that H_4R antagonists are being proposed as new anti-inflammatory/anti-allergic drugs and that most of the therapeutically available drugs for inflammation and pain are endowed with significant gastric and intestinal toxicity (137, 138).

8. ACKNOWLEDGEMENTS

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Abbreviations: ANOVA: Analysis of variance; COX-2: Cyclooxygenase-2; ECL: enterochromaffin like; GI: gastrointestinal; H_1R: Histamine H_1 receptor; H_2R: Histamine H_2 receptor; H_3R: Histamine H_3 receptor; H_4R: Histamine H_4 receptor; HDC: Histidine decarboxylase; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; RT-PCR: Reverse transcription-polymerase chain reaction; TNBS: Trinitrobenzene sulphonic acid; VEGF: Vascular endothelial growth factor

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