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Review

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The Histamine H_4 Receptor: A Novel Target for Safe Anti-inflammatory Drugs?

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ABSTRACT

The functional role of histamine H_4 receptors (H_4Rs) in the Gastrointestinal (GI) tract is reviewed, with particular reference to their involvement in the regulation of gastric mucosal defense and inflammation. H_4Rs have been detected in different cell types of the gut, including immune cells, paracrine cells, endocrine cells and neurons, from different animal species and humans; moreover, H_4R expression was reported to be altered in some pathological conditions, such as colitis and cancer. Functional studies have demonstrated protective effects of H_4R antagonists 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.

KEYWORDS: Histamine H_4 receptor; Stomach; Intestine.

ABBREVIATIONS: CNS: Central Nervous System; GI: Gastrointestinal; H_3Rs: H_3 Receptors; H_4Rs: H_4 Receptors; IBD: Inflammatory Bowel Disease; IBS: Irritable Bowel Syndrome; IL-6: Interleukin-6; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; TNBS: Trinitrobenzene Sulphonic Acid; TNF-α: Tumour Necrosis Factor-alpha; UC: Ulcerative Colitis.

INTRODUCTION

After the discovery of histamine H_2 receptors and their revolutionary role in the therapy of gastroduodenal ulcer,[1-3] the research on Gastrointestinal (GI) histamine was considered to be settled. However, renewed interested in the amine emerged in the '90s with the discovery of the histamine H_3 receptor (H_3R),[4,5] and subsequently, in the early 2000 when the H_4 receptor (H_4R) was detected from the human genome database by several independent groups.[6-8] As a consequence, novel therapeutic fields have been unravelled for antihistamine drugs: whereas histamine H_3R antagonists may represent new therapeutic options for cognitive, sleep and memory disorders[5,9] and for obesity,[10] H_4R antagonists are currently the object of intensive research, as potential candidates in the therapy of allergy, inflammatory disorders, neurophatic pain and pruritus.[7,11,12]

The present review will focus on the location and functional role of H_4Rs in the GI tract and the potential clinical implications for human diseases. Beneficial effects of H_4R blockers at GI level would be of particular interest, when considering that the available Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are still endowed with significant gastric and intestinal toxicity.[13-14] This is particularly true for the still unrecognized NSAID-induced enteropathy, which occurs frequently and still awaits for medical treatment.[15-16]

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THE HISTAMINE H_4R

The H_4R is a G-protein coupled receptor which has been primarily detected outside the Central Nervous System (CNS), and, in particular, in immune and inflammatory cells, including mast cells, eosinophils, basophils, dendritic cells and T cells.[6-8] This has led to hypothesize for the H_4R a key role in inflammation and immunoregulation. Indeed, a variety of *in vitro* data have shown that H_4Rs are involved in the control of chemotactic response and cytoskeletal changes of human eosinophils, mast cell chemotaxis and release of interleukin-16 from human CD8+ T cells and dendritic cell migration.[7-8,17] Functional *in vivo* studies in rodents have confirmed anti-inflammatory, antihyperalgesic and antiallergic effects of selective H_4R antagonists in a variety of acute and chronic experimental models.[18-24]

HISTAMINE H_4R LIGANDS

Since H_3R and H_4R are closely related, the early physiopharmacological characterization of the H_4R was based on compounds retaining the ability to bind the H_3R subtype.[25] The first selective H_4R antagonist was the indolylpiperazine compound, JNJ7777120, which displayed high affinity (K_i= 4 nM) for the human H_4R with and a >1000-fold selectivity over the other histamine receptors,[26] thus becoming the "reference" H_4R ligand in most experimental assays, also due to the lack of highly selective H_4R agonists.[27,28] To complicate matters, the subsequent availability of chemically different H_4R ligands showed that several compounds could display a protean activity, behaving as full agonists, partial agonists or actually neutral antagonists, depending on the functional assay.[29-32] Indeed, some pharmacological discrepancies have recently emerged: H_4R activation, rather than blockade, was found to display anti-inflammatory or protective effects,[30-32] and on the other hand, the "standard" H_4R antagonist JNJ7777120 was found to behave as an agonist in some experimental assays.[29-31] The use of non selective compounds (i.e. mixed H_3/H_4 receptor ligands) and the occurrence of strain-dependent effects of H_4R ligands[33] may further contribute to an erroneous interpretation of experimental data and make the characterization of H_4R function a great challenge for histaminologists. Human studies are therefore highly recommended. Unfortunately, so far, only few compounds have entered into clinical trials: JNJ-39758979 in phase II for itch and asthma, ZPL-38937887 (PalauPharma) in phase I, UR-63325 (PalauPharma) in phase I with excellent safety and profile.[34]

LOCATION OF H_4Rs IN THE GI TRACT

H_4R expression was found throughout the GI tract of different animal species and humans.[35] As shown in Table 1, the expression was unraveled both in normal tissues and under pathological conditions, such as esophagitis and colitis;[36-49] a decrease in H_4R density was reported in human gastric and colorectal carcinoma.[39,55-56] Cell types expressing H_4R include immune and inflammatory cells, epithelial cells and neurons of the myenteric and submucous plexus. Interestingly, H_4R expression was found in ghrelin-producing cells of the rat stomach,[37] leading to speculation about a possible role of histamine in the secretion of the orexigenic peptide.

Tissue	Normal/Pathological	Species	Ref.
Oesophagus	eosinophilic esophagitis	guinea pig	36
Stomach	normal	rat	37
	normal	human	38, 39
	carcinoma	human	39
Small intestine	normal	mouse	40
	normal	rat	41
	normal	dog	42
	normal	human	38,43-47
Colon	spontaneous colitis	mouse	48
	TNBS colitis	mouse	49
	normal	rat	41
	normal	dog	50
	normal	pig	51
	normal	monkey	52,53
	normal	human	44,47,54,55
	carcinoma	human	54-56
Rectum	carcinoma	human	54-56

H_4R= H_4 receptor; GI= Gastrointestinal; TNBS= Trinitrobenzene Sulphonic Acid

Table 1: Expression of histamine H_4Rs in the GI tract

GI EFFECTS OF H_4R LIGANDS

The functional data reported in intact animals with the available H_4R antagonists are summarized in Table 2.[35]

Pathological condition	Species	Ref.
Indomethacin-induced gastric damage	rat, mouse	57,58
TNBS-induced colitis	rat	59-61
Zymosan-induced peritonitis	mouse	19,21,24,62-64
Radiation-induced intestinal damage	rat	65
Ischemia-induced intestinal damage	rat	66
TNBS-induced visceral hypersensitivity	rat	67

H_4R= H_4 receptor; GI= Gastrointestinal; TNBS= Trinitrobenzene Sulphonic Acid

Table 2: Protective effects of histamine H_4R antagonists in the GI tract

In rodents the reference H_4R antagonist JNJ7777120 was unable to damage the gastric mucosa per se, even at the highest anti-inflammatory doses and, actually, it was able to reduce the gastric damage induced by indomethacin[57,58] in two models which are widely used to unravel either gastric damage or protection.[13] The gastroprotection induced by H_4R blockade was unrelated to antisecretory effects or alteration in GI motility;[35] moreover, it was found to differ from that induced by activation of H_3Rs, since it was not evidenced against necrotizing agents, such as concentrated acid.[68] Indeed, the extensive damage induced by concentrated acid (>0.35 N) is only prevented by "true" cytoprotective drugs,

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like prostaglandins[14] or by mechanisms activating cellular defense, such as re-epithelization and cell proliferation.[69] It is thus more plausible to hypothesize a selective interference of H_4R antagonists in the widely recognized mechanism underlying NSAID-induced gastric damage, i.e. accumulation and activation of neutrophils in the gastric microvasculature.[70] In line with this, in several experimental models of intestinal damage, H_4R antagonists were able to reduce neutrophil infiltration in intestinal mucosa.[19,21,24,62-64]

The gastric safety of H_4R antagonists could be of major interest, when considering that the available anti-inflammatory drugs are still endowed with gastric toxicity;[14] nevertheless, the precise role of H_4R in the gastric mucosa remains to be proven, since data with selective ligands are intriguing: the H_4R agonist VUF8430[28] was paradoxically as effective as the antagonist JNJ7777120 in reducing indomethacin-induced lesions in the rat.[57]

The protective effect reported by Varga et al.[59] in a model of acute colitis induced by Trinitrobenzene Sulphonic Acid (TNBS) seems deemed of interest, when considering that this model resembles the human Crohn's disease under macroscopic, histopathological and immunological aspects.[71] In this assay, JNJ7777120 was able to reduce macroscopic damage, neutrophil infiltration and the production of both Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6), two cytokines that play a critical role in the pathogenesis of human disease.[59-60] Several groups have underlined the increase in histamine content in mucosal biopsies from Crohn's disease, Ulcerative Colitis (UC) and food allergy;[72-73] moreover, mast cells in colonic mucosal biopsies from IBS patients were found to release more histamine than in normal subjects.[73] The recent observation that histamine H_4Rs, together with H_1Rs, contribute to the postinflammatory visceral sensitivity in the TNBS-induced colitis assay,[67] leads to hypothesize that H_4R antagonists may be of therapeutic value in various pathological conditions with abdominal pain.

Finally, a possible role of histamine H_4Rs in cancer has been recently reviewed.[74] Recent studies have evidenced the presence of H_4Rs in gastric and colorectal tumor cells and a reduction of H_4R density has been observed, which parallels the cancer progression.[54,55,56] However, functional data with histamine and H_4R ligands are contradictory, with both stimulation and/or inhibition of cell proliferation and cell growth being observed.[74]

CONCLUSIONS

The protective effects displayed by some H_4R antagonists in a variety of experimental *in vivo* models suggest that histamine H_4R blockade is not deleterious for the GI tract and can actually activate gastric and intestinal mucosal defense mechanisms, at least in rodents. Despite these favourable premises, H_4R pharmacology is still intriguing and clinical studies are mandatory in order to assess the potential benefit of H_4R antagonists in human GI disease. A careful validation of experimental assays, ligand selectivity and antibody specificity is of key importance to unravel the location and functional role of H_4Rs in the GI tract, and the therapeutic value of drugs targeting this receptor in the human pathology.

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