

COST WORKSHOP
Histamine H₄ Receptor
Where we are and where we are going...

January 29th - 30th, 2010

Military Department of Forensic Medicine, Caserma Redi, Via Venezia 5 - 50129, Florence, Italy

January 29th, 2010

13:00-15:00 Registration of participants and formalities for the European Community

14:45-15:00 **Gian Franco Gensini** (Dean of Florence Medical School)
Mario Maida (Director of Military Department of Forensic Medicine)
Emanuela Masini (President of COST Workshop)
Welcome to the participants

15:00-17:00 Receptor and drug discovery

Chairmen: Paul Chazot (UK) and **Gabriella Coruzzi** (IT)

Speakers: 30 min. each (25 min. presentation plus 5 min. discussion)

15:00 **Rob Leurs** : "*From fragments to new histamine H₄R antagonists*"

15:30 **Kerstin Sander**: "*New insights in histamine H₄Receptors ligands*"

16:00 **Elke Schneider**: "*H₄ histamine receptors mediate cell cycle arrest in growth factor-induced murine and human hematopoietic progenitor cells*"

16:30-17:00 Free presentations (15 min. each)

16:30 **Hubert Schwelberger**: "*Histamine signaling and metabolism associated with ischemia/reperfusion during solid organ transplantation*"

16:45 **Agnieszka Fogel**: "*Regional blood flow regulation in rat model of ulcerative colitis; histamine receptors involved*"

17:00-17:15 Coffee break

17:00-18:30 COST Member Meeting and WG2 Meeting

20:30 Dinner at Villa Viviani

January 30th, 2010

9:00-10:30 *From receptors to function*

Chairmen: Patrizio Blandina (IT) and Katherine Tiligada (GR)

Speakers: 30 min. each (25 min. presentation plus 5 min. discussion)

9:00 **Paul L. Chazot:** *“Expansion of the physiological roles subserved by the histamine H₄ receptor and their potential therapeutic exploitation: anatomical and functional evidence”*

9:30 **Pertti Panula:** *“Histaminergic regulation of brain endothelial cells”*

10:00 **Beatrice Passani:** *“Histamine and neuroprotection”*

10:30-11:00 Coffee break

11.00- 13.15 *Role of H₄ agonists and antagonists in inflammatory diseases*

Chairmen: Madeleine Ennis (UK) Pertti Panula (FI)

11:00 **Madeleine Ennis:** *“H₄ receptors and lung disease”*

11:30 **Katherine Tiligada:** *“The H₄Receptor in arthritic disorders”*

12:00 **Bernhard Gibbs:** *“Therapeutic approaches for targeting basophils in allergy”*

12:30 **Gabriella Coruzzi:** *“Histamine And The Stomach: Damage or Protection?”*

13:00 **Alfredo Vannacci & Alessandra Pugi:**
“Pharmacovigilance issues in anti-histamines research”

13.15-13.30 Patrizio Blandina and Emanuela Masini
Closure of the workshop

13.30-14.30 Lunch

Titles and Authors of oral presentations

FROM FRAGMENTS TO NEW HISTAMINE H₄R ANTAGONISTS

Rob Leurs¹, Maristella Adami², Rogier Smits³, Herman Lim³, Obbe Zuiderveld¹, Iwan de Esch¹ and Gabriella Coruzzi²

¹Leiden/Amsterdam Centre for Drug Research, VU University Amsterdam, 1081 HV, Amsterdam, The Netherlands ²Department of Human Anatomy, Pharmacology and Forensic Medicine, 43100 Parma, Italy; and ³Griffin Discoveries, Amsterdam, the Netherlands.

Soon after the discovery of the histamine H₄ receptor in the human genome, this new G-protein coupled receptor has been identified as a new potential therapeutic target for various inflammatory conditions, including e.g. allergic rhinitis and pruritis. To establish the full potential of H₄ receptor ligands as future therapeutics, several labs, including ours have been searching for new selective agonists and antagonists.

Following a fragment-based hit finding program we have identified various small scaffolds with (sub)micromolar affinity for the human H₄ receptor, as measured by [³H]histamine radioligand binding studies. Medicinal chemistry efforts allowed us to optimize the fragments rapidly to various quinoxaline-, aminopyrimidine-, and quinazoline analogues with low nanomolar affinity at the human H₄ receptor. These various new scaffolds are currently undergoing further analysis for their role as pharmacological tools and potential new drugs.

NEW INSIGHTS IN HISTAMINE H4 RECEPTOR LIGANDS

Kerstin Sander¹, T. Kottke, E. Proschak, G. Schneider, H. Stark

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The number of histamine H4 receptor (H4R) ligands has increased nearly exponentially since the discovery of the reference H4R antagonists JNJ-7777120. The main structural classes that might provide first clinical candidates are related carboxamides and analogue compounds, (fused) aminopyrimidines and arylimidazoles.¹ However, structural determinants of H4R ligand affinities and efficacies are far from being fully clarified. A loose construction pattern has been identified but without differentiating functionalities.²

In addition to other labs we identified two classes of H4R ligands, namely (imidazolyl)alkyl derivatives and 2,4-diaminopyrimidines, by in-house library search and virtual screening/de novo design, respectively. Both series of compounds showed remarkable structure-affinity- and especially -efficacy-relationships. Efficacies ranging from partial agonism to inverse agonism were determined by means of [³⁵S]GTP γ S binding assays.

Efficacies in the (imidazolyl)alkyl class are defined by the character of an alkyl linker within the given structure, whereas affinities can largely be modified by variation of the alkyl rests. Within the series of diaminopyrimidines the substitution site of a benzyl moiety has a major influence on affinity and efficacy.³ Conclusions drawn from these relationships for improved pharmacological tools will be discussed taking into account the characterization of the H4R binding pocket.

[1] Engelhardt H, Smits RA, Leurs R, Haaksma E, de Esch IJ. A new generation of anti-histamines: Histamine H4 receptor antagonists on their way to the clinic. *Curr. Opin. Drug. Discov. Devel.* 2009, 12, 628-643.

[2] Tanrikulu Y, Proschak E, Werner T, Geppert T, Todoroff N, Klenner A, Kottke T, Sander K, Schneider E, Seifert R, Stark H, Clark T, Schneider G. Homology model adjustment and ligand screening with a pseudoreceptor of the human histamine H4 receptor. *ChemMedChem* 2009, 4, 820-827.

[3] Sander K, Kottke T, Tanrikulu Y, Proschak E, Weizel L, Schneider EH, Seifert R, Schneider G, Stark H. 2,4-Diaminopyrimidines as histamine H4 receptor ligands - scaffold optimization and pharmacological characterization. *Bioorg. Med. Chem.* 2009, 17, 7186-7196.

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H₄ HISTAMINE RECEPTORS MEDIATE CELL CYCLE ARREST IN GROWTH FACTOR-INDUCED MURINE AND HUMAN HEMATOPOIETIC PROGENITOR CELLS

Elke Schneider

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France

The preferential expression of the H₄ histamine receptor (H₄R) in the bone marrow prompted us to address its role during hematopoiesis. We found that both murine and human progenitor cell populations express this receptor subtype on transcriptional and protein levels and respond to its agonists by reduced growth factor-induced cell cycle progression that leads to decreased myeloid, erythroid and lymphoid colony formation. H₄R activation prevents the induction of cell cycle genes through a cAMP/PKA-dependent pathway that is not associated with apoptosis. It is mediated specifically through H₄R signaling since gene silencing or treatment with selective antagonists restores normal cell cycle progression. The arrest of growth factor-induced G₁/S transition protects murine and human progenitor cells from the toxicity of the cell cycle-dependent anticancer drug Ara-C in vitro and reduces aplasia in a murine model of chemotherapy. This first evidence for functional H₄R expression in hematopoietic progenitors opens new therapeutic perspectives for alleviating hematotoxic side effects of antineoplastic drugs.

HISTAMINE SIGNALING AND METABOLISM ASSOCIATED WITH ISCHEMIA/REPERFUSION DURING SOLID ORGAN TRANSPLANTATION

Hubert G. Schwelberger

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Early allograft dysfunction as well as long-term graft loss still represent major obstacles to successful organ transplantation. Besides immunological reactions due to donor and recipient incompatibility, ischemia/reperfusion injury of the transplanted organ is the major process negatively affecting allograft function early after transplantation and long-term graft survival. Previously we have been studying ischemia/reperfusion associated damage of grafted organs in mouse and rat models of heart and kidney transplantation and in patients, focusing on new biomarkers for early detection of graft damage and on cytokine and chemokine signaling leading to infiltration of inflammatory cells into the graft. Although the role of histamine in ischemia and reperfusion has been studied in various animal models its specific role in solid organ transplantation has only been poorly explored. Therefore, we would like to apply established procedures but also new techniques emerging from COST Action BM0806 to explore histamine signaling through the different histamine receptors and receptor subtypes and its metabolism in the course of solid organ transplantation.

Besides a huge collection of RNA, cDNA, protein and histochemical samples from numerous syngeneic and allogeneic animal transplantation experiments with short-term and long-term follow-up that are ready to use for expression and protein localization experiments, the well-established models can easily be adapted for investigating treatment with specific histamine receptor agonists and antagonists and for testing of various gene knockout settings. Furthermore, our collection of tissue and body fluid samples from patients undergoing solid organ transplantation facilitates comparison of results obtained in animal studies with the situation in humans.

REGIONAL BLOOD FLOW REGULATION IN RAT MODEL OF ULCERATIVE COLITIS; HISTAMINE RECEPTORS INVOLVED

Agnieszka Wiesława Fogel¹, Katarzyna. Kiec-Kononowicz², Barbara Skrzydło-Radomska³ and Jerzy Jochem⁴

¹Department of Hormone Biochemistry, Medical University of Lodz ²Department of Technology and Biotechnology of Drugs, Medical College of Jagiellonian University of Cracow ³Chair and Clinic of Gastroenterology, Medical University of Lublin and ⁴Department of Basic Medical Sciences, Bytom, Medical University of Silesia, Poland.

Histamine is implicated in various functions of the gastrointestinal tract, including the regulation of gastric acid secretion, fluid and electrolyte transport and modulation of the enteric nervous system. Many studies demonstrate an involvement of histamine in the pathogenesis of inflammatory bowel diseases (IBD). In patients with IBD, colonic mast cells are closer opposed to neurons, more densely packed and release more histamine than in normal subjects. The mast cell location and histamine release correlate with the symptom score in these patients. In experimentally induced colonic lesions in rats histamine H₁, H₂ and mixed H_{3/4} receptor antagonists ketotifen, ranitidine and thioperamide, respectively, administered repeatedly, positively influenced the disease course. Available literature indicates that, when released from activated mast cells, histamine may induce vasodilatation of mesenteric arteries. The present study was undertaken to examine regional haemodynamic and biochemical effects of histamine H₁–H₄ receptor antagonists in rats with TNBS-induced colitis. The following drugs were accordingly employed: ceterizine (10mg/kg), ranitidine (10mg/kg), DL-76 (6mg/kg) and JNJ 7777120 (10mg/kg). The compounds were given by sc route for 7 days. The colonic haemodynamics measurement was performed after the therapy completion. The inferior mesenteric artery blood flow (IMBF) was measured in anaesthetised animals by a Transit Time Flowmeter type 700 with an electrode type 1RB (Hugo Sachs Elektronik, Germany). As expected, in the rats with colitis, IMBF was significantly higher than in healthy controls, i.e., 3.55 ± 0.87 vs. 1.86 ± 0.69 ml/min ($p < 0.05$). Only in the colitic-DL-76 treated rats, was IMBF similar to that in the control ones, being 2.37 ± 0.67 ml/min ($p < 0.05$), the effect was lesser in the ranitidine- or ceterizine-treated rats, whereas in the rats treated with JNJ 7777120, IMBF did not differ from the untreated colitic rats, amounting to 3.43 ± 0.74 ml/min. The inflammatory indices- macroscopic mucosal damage score, as well as mucosal myeloperoxidase activity, were lower in DL-76 treated colitic rats than in the other colitic rats- both, untreated and treated, indicating benefits of anti-H₃ receptor therapy. In conclusion, the results suggest that histamine H₃, rather than H₄ receptors, participate in regional blood flow regulation in rat model of ulcerative colitis. This is compatible with the presence of H₃ receptors in the intestine.

EXPANSION OF THE PHYSIOLOGICAL ROLES SUBSERVED BY THE HISTAMINE H₄ RECEPTOR AND THEIR POTENTIAL THERAPEUTIC EXPLOITATION: ANATOMICAL AND FUNCTIONAL EVIDENCE

Paul L. Chazot

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The recently identified histamine H₄ receptor (H₄R) has attracted much interest because of its multiple functions and potential therapeutic exploitation. Until relatively recently, the H₄R was thought to be expressed exclusively on haematopoietic cells, suggesting a prominent role in immune responses and inflammatory processes. However, based on the development of selective immunological and pharmacological tools, the H₄R has been shown also to be expressed on an expanding range of cell types, including defined populations of rodent endocrine cells in the GI tract, human malignant lung and breast carcinomas, rodent and human salivary gland acinar and intercalated duct cell types, rodent and human enteric nerves, subpopulations of rodent and human spinal dorsal sensory, dorsal root ganglia and ventral motor neurons, and to be functionally expressed in the CNS on defined cortical neurons, indicating a more extensive biological role in a range of non-haematopoietic cells. Key therapeutic arenas in which the H₄R is expected to impact based on these new findings include chronic inflammatory disorders, autoimmune disorders, asthma, itch, ulcers, neuropathic pain and cancers. I will review the anatomical and functional evidence which supports these new non-immunological roles for the H₄R.

HISTAMINERGIC REGULATION OF BRAIN ENDOTHELIAL CELLS

Pertti Panula¹, Rob Leurs² and Kaj Karlstedt³

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Histamine H1 and H2 receptors are known regulators of brain endothelial cells and permeability. Both are expressed in rat brain endothelial cells and downregulated by dexamethasone in vitro (Karlstedt et al. 1999). We studied the expression of H3 and H4 receptors in rat endothelial cells in vitro and found both to be expressed. Expression of H4R mRNA was upregulated by dexamethasone. Histamine induced MAPK activation which was sensitive to JNJ777120, a specific H4R antagonist, but not ciproxifan, a specific H3R antagonist. The results suggest that H4 receptor in may regulate brain endothelial functions.

Karlstedt, K., Sallmen, T., Eriksson, K.S., Lintunen, M., Couraud P-O., Joo, F., and Panula, P.: Lack of histamine synthesis and down-regulation of H1 and H2 receptor mRNA levels by dexamethasone in cerebral endothelial cells. *J. Cerebr. Bl. Fl. Metab.* 19:321-330, 1999.

HISTAMINE AND NEUROPROTECTION

M. Beatrice Passani

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The possible neuroprotective effect of brain histamine and its receptors ligands has not received much attention, despite the growing interest in developing histaminergic therapeutics to treat neurodegenerative diseases. Recent, elegant results suggest that histaminergic neurons protect the developing hippocampus from kainic acid-induced neuronal damage in an organotypic coculture system. The regulation of neuronal survival is supposedly mediated, at least in part, through histamine H₁ and H₃ receptors [1]. Further evidence indicates that activation of the H₃ receptor may be implicated in neuroprotection was provided by the same group as H₃ receptor mRNA is up-regulated following induction of cerebral ischemia [2] or kainic acid induced seizures in the rat [3]. We recently demonstrated that H₃ receptor agonists protect cultured murine neurons from neurotoxic insults and apoptosis, by activating the Akt/GSK3 β pathway, increasing the expression of antiapoptotic factors such as Bcl-2 and decreasing the expression of proapoptotic caspases [4]. The H₄ receptor is expressed in the cells of the immune system that mediate brain inflammatory responses. Hence, we intend to test the consequences of H₄ receptor inhibition in the experimental allergic encephalomyelitis, a murine model of the autoimmune CNS inflammatory disease multiple sclerosis.

All together, these results and proposals are uncovering a novel role of the brain histaminergic system that may impact on the development of new treatments for brain diseases.

[1]Kukko-Lukjanov TK, Soini S, Taira T, Michelsen KA, Panula P, Holopainen IE (2006) *J Neurosci* 26:1088-97.

[2]Lozada A, Munyao N, Sallmen T, Lintunen M, Leurs R, Lindsberg PJ, Panula P. (2005) *Neuroscience* 136:371-9

[3]Lintunen M, Sallmen T, Karlstedt K, Panula P. (2005) *Neurobiol Dis.* 20:155-69.

[4]Mariottini C, Scartabelli T, Bongers G, Arrigucci S, Nosi D, Leurs R, Chiarugi A, Blandina P, Pellegrini-Giampietro DE, Passani MB. (2009) *J Neurochem* 110:1469-78.

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H₄ RECEPTORS AND LUNG DISEASE

Madeleine Ennis

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H₄ receptors were cloned in a number of different laboratories around 2000. Both message and protein are found in cells of the immune system such as mast cells, natural killer cells, monocytes, dendritic cells and eosinophils. Antagonists of the H₄ receptor have profound effects on these cells such as inhibiting histamine-induced chemotaxis. Thus the H₄ receptor could be a key player in the innate immune system.

In this talk I will review works showing the role of the H₄ receptor in airways disease (asthma) and also postulate some other diseases where it might play a role. Atopic asthma is characterised by eosinophilia in the bronchoalveolar lavage fluid (BAL). In an acute murine asthma model, either the use of H₄ receptor knockout mice or an H₄ antagonist resulted in a reduction of total BAL cells and BAL eosinophils [1]. In contrast a recent study showed that the combination of an H₁ and H₄ receptor antagonist resulted in a synergistic inhibition of the eosinophilia, although both compounds alone were without significant effect. This suggests that the development of compounds with combined H₁ and H₄ efficacy could be useful [2]. A further characteristic of asthma is airway hyperreactivity; intratracheal administration of an H₄ agonist not only reduced airway hyperreactivity but also reduced inflammation [3]. In the nose the presence of both H₁ and H₄ receptors is raised in nasal polyp tissue compared to that from nasal turbinate [4]. We have also managed to demonstrate the presence of H₄ receptors on nasal epithelial cells. Airway epithelial cells are much studied in diseases such as cystic fibrosis and COPD, both situations where there are frequent infections. The function of H₄ receptors on airway epithelial cells remains to be investigated.

[1] Morgan RK, McAllister B, Cross L, Green DS, Kornfeld H, Center DM, Cruikshank WW. Histamine 4 receptor activation induces recruitment of FoxP3⁺ T cells and inhibits allergic asthma in a murine model. *J Immunol.* 2007 Jun 15;178(12):8081-9.

[2] Deml KF, Beermann S, Neumann D, Strasser A, Seifert R. Interactions of Histamine H₁-Receptor Agonists and Antagonists with the Human Histamine H₄-Receptor. *Mol Pharmacol.* 2009 Aug 31. [Epub ahead of print]

[3] Dunford PJ, O'Donnell N, Riley JP, Williams KN, Karlsson L, Thurmond RL. The histamine H₄ receptor mediates allergic airway inflammation by regulating the activation of CD4⁺ T cells. *J Immunol.* 2006 Jun 1;176(11):7062-70.

[4] Jókúti A, Hellinger E, Hellinger A, Darvas Z, Falus A, Thurmond RL, Hirschberg A. Histamine H₄ receptor expression is elevated in human nasal polyp tissue. *Cell Biol Int.* 2007 Nov;31(11):1367-70.

THE H₄ RECEPTOR IN ARTHRITIC DISORDERS

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Arthritic disorders, such as osteoarthritis and rheumatoid arthritis (RA), are painful chronic conditions that have a significant impact on individuals, families and society, resulting in overall poor quality of life and socioeconomic constraints. Current pharmacological treatment targets pain control and includes analgesics and non-steroidal anti-inflammatory drugs, many of which are beset with serious side effects. Future treatment modalities are geared toward more effective therapeutic approaches that hopefully would be able to reverse the disease process. The characterisation of the H₄ as the immune system histamine receptor suggests that it may be a promising target for the development of novel therapeutic agents in arthritis [1,2]. Although a recent report argued for the anti-inflammatory properties of histamine in RA, the amine has been largely regarded as a pro-inflammatory mediator in arthritic disorders, while evidence from human and experimental studies supports the contribution of the H₄ receptor in the disease phenotype. Additionally, cross-talk of histamine receptor subtypes in the underlying (patho)physiological pathways should not be ruled out. The interplay between H₁, H₃ and H₄ receptors needs careful consideration, since a number of selective ligands have shown efficacy in various experimental models of inflammation and nociception. Interestingly, arthritis-associated inflammation may alter vascular responses that contribute to the systemic manifestations of the disease, as common mechanisms seem to be involved in chronic inflammatory processes, immune dysregulation and cardiovascular manifestations. To date, evidence for the contribution of H₄ receptor in a putative automodulatory function of histamine in extra-articular cartilage and in peripheral blood vessels has been obtained using the selective H₄ receptor antagonist JNJ7777120 in a rat model of adjuvant arthritis [3-5]. Although the systemic localisation and functional characterization of the H₄ receptor remains largely elusive, the data provide the lead for ongoing research on its systemic function that may prove beneficial in understanding the complex pathophysiology of the arthritic phenotype and in providing useful tools for more effective therapeutic strategies.

- [1] Tiligada E, Zampeli E, Sander K, Stark H (2009) Histamine H₃ and H₄ receptors as novel drug targets. *Expert Opin Investig Drugs* 18:1-13
- [2] Zampeli E, Tiligada E (2009) The role of histamine H₄ receptor in immune and inflammatory disorders. *Br J Pharmacol* 157:24-33
- [3] Zampeli E, Thurmond RL, Tiligada E (2008) Effect of the H₄R antagonist JNJ7777120 on the cartilage histamine content in rats with adjuvant arthritis. *Fund Clin Pharmacol* 22(S2):10, S5.C001
- [4] Zampeli E, Kyriakidis K, Tiligada E (2009) Differential effects of H₁ and H₄ receptor antagonists on the cartilage histamine content in rats with adjuvant arthritis. *Proceeding of the 38th EHRS Annual Meeting*, P25
- [5] Kyriakidis K, Zampeli E, Tiligada E (2009) Effect of the H₄ receptor antagonist JNJ7777120 on histamine levels of peripheral blood vessels in rats with adjuvant arthritis. *Proceeding of the 38th EHRS Annual Meeting*, O28

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THERAPEUTIC APPROACHES FOR TARGETING BASOPHILS IN ALLERGY

Bernhard F. Gibbs

Medway School of Pharmacy, University of Kent, Chatham Maritime, UK.

There is increasing evidence to demonstrate a role for basophils in allergy, not only as effector cells during late-phase responses and chronic allergic inflammation but also as immunomodulators that support underlying Th2 immunity associated with allergies. Basophils contribute to the symptoms of allergic inflammation by releasing histamine and leukotriene-C4 following allergen stimulation, an ability that is also shared by mast cells, which are more numerous than basophils. However, in humans, basophils but not mast cells also rapidly produce IL-4 and IL-13, which upregulate Th2 immunity, increase IgE synthesis and enhance vascular cell adhesion molecule expressions. Targeting basophil mediator generation may therefore serve as a promising therapeutic approach, particularly in view of preventing their numerous immunomodulatory tasks that support allergies. Like many of their mast cell counterparts, the functions of basophils may be inhibited by agents that elevate intracellular cAMP levels, such as beta-2-receptor agonists and methylxanthines. Calcineurin inhibitors also block both basophil and mast cell activation. However, unlike mast cells, basophil mediator release is also affected by glucocorticoids but not by cromoglycate-like drugs, which instead target mucosal-like human mast cell populations. More recent inhibitory strategies include engagement of receptors that lead to increased involvement of inhibitory phosphatases, such as SHIP, leading to rapid functional desensitization, as well as possibly impeding basophil and mast cell trafficking using H4-receptor antagonists. It is hoped that by preventing the movement of basophils from the circulation to tissues affected by allergic inflammation as well as rapidly desensitizing basophils to further allergen-mediated stimulation this may lead to more effective management of allergic diseases.

HISTAMINE AND THE STOMACH: DAMAGE OR PROTECTION?

Gabriella Coruzzi, Maristella Adami

Department of Human Anatomy, Pharmacology and Forensic Medicine, University of Parma, Italy

The gastric effects of histamine have been known since the beginning of the last century (1910) and include activation of gastric acid secretion and vasodilatation; however, only in 1972 the physiological importance of the amine in the stomach was assessed, due to the discovery of histamine H₂ receptors and the consequent revolution in the therapy of ulcer disease. The discovery of histamine H₃ receptors (H₃R) in 1983 unravelled gastroprotective effects of histamine, since selective H₃R agonists proved to enhance gastric mucosal defence in different rat ulcer models. Finally, H₄ receptors (H₄R) were cloned at the beginning of this century, which are involved in the inflammatory and immune effects of histamine. Immunohistochemistry studies detected H₄R expression in some cells of rodent and human gastrointestinal (GI) tract, including neurons of the myenteric and submucous plexus and ghrelin-producing cells. However, functional studies with selective H₄R ligands are controversial, since, gastroprotective effects were observed either with agonists or antagonists, depending on the experimental ulcer model. These data indicate that histamine may have different roles in the gastric mucosa, depending on the type of receptor involved; interestingly, histamine seem to be involved in the gastroprotective effects of the orexigenic peptide ghrelin, thus suggesting new aspects in the complex integrated network that regulates gastric mucosal defence.

PHARMACOVIGILANCE ISSUES IN ANTI-HISTAMINES RESEARCH

Alfredo Vannacci, Alessandra Pugi

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Adverse drug reactions (ADRs) are considered among the leading causes of morbidity and mortality. Spontaneous reporting of ADRs has become an important component of monitoring and detecting specific drug related issues. Anti-H₁ antihistamines are a widely used both in children and adults and are usually considered as safe. Drug-related sedation is the major limitation to the use of first generation antihistamines. New molecules, called “non-sedating” antihistamines, have been synthesized and marketed in the last three decades. They have a more favorable risk-benefit ratio with regard to the CNS-depressant adverse effects. However two early second generation antihistamines, terfenadine and astemizole, which are no longer approved, were found to be associated with unexpected cardiac adverse reactions. Those effects result from the prolongation of QT interval, that may lead to serious and life-threatening ventricular arrhythmias, in particular torsade de pointes, through the inhibition of the I_{Kr} channel. Risk significantly increases when these drugs are used in predisposed patients, at high dosages or with concomitant CYP450 inhibitors. Cardiac toxic effects related to antihistamine treatment occur rarely, in view of the widespread use of the drugs; such rare events can hardly be detected during clinical trials, but could be more easily observed in the post-marketing phase through spontaneous reporting systems. The total amount of spontaneous adverse events reports related to systemic use of antihistamines (ATC: R06A), recorded in the Italian National Pharmacovigilance Database (since 2001), is 288 ADRs. Among them, 30 were defined as “cardiac disease” (System Organ Class): 5 (16.7%) were reported as “severe” and 18 (60%) as “mild”. No fatal case was observed. Agents most commonly involved are desloratadine, levocetirizine and cetirizine. A case of desloratadine-induced QT prolongation was also observed. In conclusion, anti-H₁ antihistamines are useful drugs whose safety profile is substantially positive; anyway, since several severe reactions were reported, a continuous post-marketing surveillance is needed.