

Scientific report – Workshop of working group 2
“Histamine H₄ Receptor: where we are and where we are going ...”

The Workshop of Working Group 2 (WG2) of the COST Action BM0806: Recent Advances in Histamine Receptor H₄ Research: where we are and where we are going ... was held during 29-30 January 2010, in Florence (Italy). The Workshop brought together 13 speakers from 10 European countries to share their knowledge about the pharmacology of the histamine receptor H₄. A total of 92 participants, including researchers, doctoral and post-doctoral fellows attended this Workshop. This meeting was also an occasion for stimulating interactions and for exchanging points of view among scientists and a great opportunity for the students to meet well known researchers in this field. The COST Workshop was formally opened (welcome to the participants) by Prof. Emanuela Masini, president of COST workshop and Prof. Pier Francesco Mannaioni, Emeritus Professor of the University of Florence. The COST workshop was divided in three main plenary sessions and the summary of each one are reported below.

“Receptor and drug discovery”

This session was chaired by Prof. P. Chazot (UK) and Prof. G. Coruzzi (IT). The first speaker was Prof. R. Leurs, (Leiden/Amsterdam Centre of Drug Discovery, University of Amsterdam, The Netherlands), who showed how medicinal chemistry studies contribute to optimization of structural scaffolds to confer (sub)micromolar affinity to histamine H₄ receptor; indeed, various quinoxaline-, aminopyrimidine-, and quinazoline analogues have low nanomolar affinity for the H₄ histamine receptor. New insights in histamine H₄ receptors ligands was the topic treated by Dr. K. Sander (Institute of Pharmaceutical Chemistry, Johan Wolfgang Goethe University, Germany) who demonstrated that two classes of H₄ receptors ligands show remarkable structure-affinity, especially structure-efficacy relationships ranging from partial agonism to inverse agonism. Dr. E. Schneider (CNRS UMR 8147, University René Descartes Hopital Necker, Paris, FR) reported that H₄ receptor activation prevents the induction of cell cycle genes through a cAMP/PKA-dependent pathway, which is not associated with apoptosis. 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. The role of histamine in solid organ transplantation was discussed by Dr. H. Schwelberger (Molecular Biology Laboratory, Medical University Innsbruck, AU). He reported that the well-established models of syngenic and allogenic animal transplantation may easily be adapted for investigating treatments with specific histamine receptor agonists and antagonists and for testing various gene knock-out settings. The last talk of this session was about the involvement of histamine receptors in a model of ulcerative colitis (Prof. A. Fogel, Dept. of Hormone Biochemistry, Medical University of Lodz, PO) showing that H₃ receptors, rather than H₄ receptors, play a role in the regulation of blood flow in a rat model of ulcerative colitis.

“From receptors to function”

The second main session of the meeting had as chairmen Prof. P. Blandina (IT) and Prof. E. Tiligada (GR). Prof. P. Chazot (Integrative Neuroscience, Durham University, UK) was the first speaker of the second day and explained the physiological role subserved by histamine H₄ receptor and its potential therapeutic exploitation. Prof. Chazot showed that the H₄ receptor is expressed on an expanding range of cell types, including defined populations of rodent endocrine cells in the gastrointestinal (GI) tract, on human malignant lung and breast cancers cells, subpopulations of rodent and human spinal dorsal sensory and CNS on well defined cortical neurons, indicating a more extensive biological role, than initially postulated. He reviewed the anatomical and functional evidence supporting these new findings for the H₄ receptor such as chronic inflammatory disorders, autoimmune disorders, asthma, ulcers, neuropathic pain and cancers. Prof. P. Panula (Neuroscience Center and Institute of Biomedicine, University of Helsinki, FI) and his group demonstrated the expression of histamine H₃ and H₄ receptors in rat endothelial cells *in vitro*. Moreover, expression of H₄ receptor mRNA is upregulated by dexamethasone, as

well as histamine induced MAPK activation which is sensitive to a specific H₄ receptor antagonist (JNJ777120), but not to an H₃ receptor antagonist (ciproxifan). The involvement of histamine in neuroprotection was reviewed by Dr. B. Passani (Dept. of Preclinical and Clinical Pharmacology, University of Florence, IT) who demonstrated that H₃ receptor agonists protect cultured murine neurons from neurotoxic insults and apoptosis, by activating the Akt/GSK3 β pathway by increasing the expression of antiapoptotic factors such as Bcl-2 and by decreasing the expression of pro-apoptotic caspases.

“Role of the H₄ agonists and antagonists in inflammatory diseases”

Prof. M. Ennis (UK) and Prof. P. Panula (FI) chaired the last plenary session of the Workshop. The session started with Prof. M. Ennis (Respiratory Medicine Research Group, The Queen’s University of Belfast, Northern Ireland, UK) reviewing works showing the role of the H₄ receptor in asthma. She reported results showing that in an acute murine asthma model, neither the use of H₄ receptor knockout mice or an H₄ antagonist resulted in a reduction of total bronchoalveolar lavage (BAL) fluid cells and BAL eosinophils (a characteristic of atopic asthma). In contrast, the combination of an H₁ and H₄ receptor antagonist resulted in a synergic inhibition of the eosinophilis, suggesting that the development of compounds with combined H₁ and H₄ efficacy may be therapeutically useful. Furthermore, intratracheal administration of an H₄ agonist not only reduced airway hyper reactivity but also reduced inflammation. Evidence for the contribution of the H₄ receptor in arthritic inflammation was presented by Prof. E. Tiligada (Dept. of Pharmacology, University of Athens Medical School, Athens, GR), although the systemic localization and functional characterization of the H₄ receptor in this pathology still remains elusive. “Therapeutic approaches for targeting basophils in allergy” was the title of the talk presented by Prof. B. Gibbs (Medway School of Pharmacy, University of Kent, Chatham Maritime, UK). He presented the hypothesis that targeting basophil mediators generation may serve as a promising therapeutic approach to treat allergy. 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, may lead to a more effective managements of allergic diseases. The session continued with Prof. G. Coruzzi (Dept. of Human Anatomy, Pharmacology and Forensic Medicine, University of Parma, IT) who presented studies regarding histamine and its function in the GI tract. Immunohistochemistry studies detected H₄ receptor expression in some cells of rodent and human GI tract, including neurons of the myenteric and submucous plexus and ghrelin-producing cells. However, functional studies with selective H₄ receptors are controversial, since gastroprotective effects were observed either with H₄ receptors agonists or antagonists, depending on the experimental ulcer model, indicating that histamine may have different roles in the gastric mucosa depending on the type of the histamine receptor involved. The Workshop was concluded with the talk entitled Phamacovigilance and anti-histaminic drugs (Dr. Vannacci, Tuscan Regional Centre of Pharmacovigilance, University of Florence, IT). The anti-histamine drugs are usually considered safe but the risk of adverse drugs reactions significantly increases when these drugs are used in predisposed patients, at high dosages or with concomitant CY450 inhibitors. This presentation stimulated a discussion on the possibility of developing new anti-histaminic drugs with fewer adverse drug reactions.

The meeting was closed with concluding remarks by Prof. P. Blandina (IT) and Prof. E. Masini (IT) and was followed by lunch.