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Recent Advances in Histamine Receptor H4R Research
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Participating countries: AT, CH, DE, DK, ES, FI, FR, GR, HU, IE, IL, IT, LT, NL, PL, SE, SI, SK, UK
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Working Group 2

Pathophysiological importance of H_4R systems

Progress Report 2010

- Identification of H_4R isoforms & elucidation of the molecular structure.
- Integration & critical evaluation of data, derived mainly from basic research, on the H_4R is principally expressed on haematopoietic cells and plays a key role in immune and inflammatory responses complex H_4R-mediated signals in various cell types & conditions.
- Elucidation of the role of the H_4R in models of allergy, inflammation, immune disorders, cancer & other conditions.

In accordance with aims of the Action, the participants of WG2 have developed basic and finalized research to evaluate the pathophysiological role of H_4R in several diseases. An *in vivo* animal model of acute bronchospasm for evaluating the role of H_4R antagonists as potential therapeutic agents in asthma therapy has been validated. In this model the effect of JNJ777120, a selective H_4R antagonist, on antigen-induced asthma–like reaction was tested. The H_4R antagonist was able to reduce the respiratory alteration as well as the inflammatory parameters modified by antigen challenge. The protective action of JNJ777120 in allergic bronchospasm was significantly increased when the animals were pretreated with fumonisin B1, an inhibitor of ceramide syntheses, indicating that a modulation of apoptotic process amplified the antiflammatory effect of JNJ777120. As *in vitro* test model for H_4R with the co-expression of different proteins was described and complemented with an acute murine asthma model, where the synergistic role of H_1R and H_4R as potential therapeutic agents in asthma was shown. Moreover, other *in vivo* animal models of inflammation have been validated, such as carrageenan-induced pleurisies, allergic encephalomyelitis and a rat model of ulcerative colitis. In this disease, H4R seem to be involved in the regulation of blood flow. In this context H_4R

antagonists can be regarded as non-conventional antinflammatory drugs, as they reduce pro inflammatory cytokine production and prostaglandins.

New information about the role of histamine in the gastric mucosa has been provided. Along this line of research the involvement of different histaminergic receptors in gastroprotection was evidenced. Furthermore histamine seems 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 defense. Innovative knowledge was obtained on the role of H4R in murine and human progenitor cell populations; these cells express H_4R 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.

WG2 has organized a workshop titled "Histamine H_4Receptor. Where we are and where we are going…", where a total of 92 participants, including doctoral and post-doctoral fellows, from 10 different countries, attended. The discussed topics were: receptors and drug discovery; from receptors to function, role of H_4R agonists and antagonist in inflammatory disease.

The members participating at the WG2 have submitted several national and international research projects. A project finalized to the study of H_4R inhibition in allergic encephalomyelitis is under evaluation. A project finalized to the study of H4R antagonists in allergic asthma and carrageenan-induced pleurisy was financed by an Italian bank foundation. Other international research proposals are under evaluation. Some of the participants at WG2 have been accepted as fellows for Short Term Scientific Missions in European Universities. Dr. Vasily Stegaev, University of Helsinki, was accepted by Prof. Andras Falus for a STSM at Semmelweis University, Budapest, Hungary. Simona Rajtar went as a post doctoral fellow for STSM at Athens University, with the tutoring of Prof. Katherine Tiligada, for a research about the effects of H_4R antagonist on the cartilaginous, vascular and esophageal histamine content. Prof. Yrjö Konttinen, University of Helsinki, established a joint project involving Paul Chazot, Pertti Panula, Andras Falus, Edit Buzas and Holger Stark.

Many members of WG2 also participated to the XXXIX Meeting of European Histamine Research Society, COST Action BM0806 that was held in Durham, UK, 21st-25th April 2010. Emanuela Masini, WG2 Leader, spoke about "Anti.inflammatory effects of a selective histamine H_4R antagonist in a rat model of carrageenan-induced pleurisy" in the Training School for ESRs. Elena S. Rivera talked about "JNJ7777120 compound: a potential candidate for use a radioprotector". Patrizio Blandina held a plenary lecture titled "Functional implications of histaminergic neurons heterogeneity", while Bernhard F. Gibbs spoke about "Differential

modulation of human basophil function by Ambroxol and related secretolytic analogues". Hubert G. Schwelberger delivered a lecture about "Histamine signaling and metabolism in solid organ transplantation". Jerzy Jochem gave a talk about "Involvement of the brain histaminergic system in the melanocortin MC4 receptor agonist RO27-3225-induced resuscitating effect in haemorrhage-shocked rats-haemodynamic studies". Gabriella Coruzzi spoke about "Involvement of histamine in the gastroprotection induced by ghrelin in the conscious rat". Wieslawa Agnieszka Fogel held a lecture about "Histamine H_3 rather than H_4 receptors, participate in regional blood flow regulation in rat model of ulcerative colitis". The last lecture was held by M. Beatrice Passani, titled "Oleoylethanolamide and brain histamine interact to regulate feeding behavior". All the members participated at a discussion in the plenary lecture and poster section.

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