

Themed Issue: Histamine Pharmacology Update

EDITORIAL

Histamine pharmacology: four years on

Paul L Chazot

*European Histamine Research Society (EHRS), School of Biological and Biomedical Sciences,
Durham University, Durham, UK*

Correspondence

Paul L Chazot, European
Histamine Research Society
(EHRS), School of Biological and
Biomedical Sciences, Durham
University, South Road, Durham,
DH1 3LE, UK. E-mail:
paul.chazot@durham.ac.uk

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The histamine field has moved on rapidly in the last four years, with expansion in roles and clinical development, particularly in the newest two of four histamine receptors. This themed volume is a testament to this expansion with 16 original and review articles spanning a wide spectrum of histamine-related topics, with therapeutic translational relevance to addiction, dementias, anxiety disorders, cancers, vestibular disorders, migraine and autoimmune disorders.

LINKED ARTICLES

This article is part of a themed issue on Histamine Pharmacology Update. To view the other articles in this issue visit <http://dx.doi.org/10.1111/bph.2013.170.issue-1>

Abbreviations

EHRS, European Histamine Research Society; ESF COST, European Science Foundation Cooperation in Science and Technology

Histamine [(2-(imidazol-4-yl) ethylamine)] is a biogenic amine that has been a favourite among pharmacologists since the inception of the discipline in the early 20th century with the classic experiments of Sir Henry Dale. It can be considered as the 'pleiotropy' master amine with key roles in cell immune defence, nutrition, neurological activity, growth, development and fertility. This themed volume is a follow-up of a highly successful volume in 2009, which was published at the beginning of European Science Foundation Cooperation in Science and Technology (ESF COST) Action BM0806 focused on histamine, particularly histamine H₄R research. This year represents the completion of this highly successful 4 year Action, which was praised by the European Union as a prime example of best practice. This volume is dedicated to the memory of two premier histaminologists who contributed profoundly to the basic and clinical pharmacology of histamine, namely Professors Sir James Black and Walter Schunack, particularly related to the pharmacology of H₂ and H₃ receptors respectively. Many members of the COST Action and the European Histamine Research Society (EHRS), including myself, have been profoundly influenced by both men, and have contributed pieces published in this present themed volume in honour of their memory. This is an exciting period as both H₃ and H₄ receptor-directed compounds have entered advanced clinical development, both targets offering promising new therapies for many largely poorly treated central

and peripheral pathologies respectively. The reviews cover a range of topical areas relating to histamine and its role in neutrophils, the latest examples of mast cell stabilizers, central histamine receptors, particularly H₃R and drug addiction, crosstalk between histamine and its aminergic cousins and finally an exciting new integrated structural chemogenomic method to define molecular and structural motifs for ligand binding and selectivity for histamine receptors, which has significant implications for the whole GPCR superfamily.

Intra- and intercellular crosstalk among histamine and amine-related components has important pathophysiological consequences, as reviewed in detail by Sánchez-Jiménez *et al.* (2013). Histamine and the immune system have a long history, with the H₁ and H₂ receptors much studied as key players. *Neutrophils* are the most abundant type of leukocyte in mammals and represent a fundamental part of the innate immune system, crucial to combat infection. Neutrophils achieve this role in various ways, including oxidative burst, which involves the rapid generation and release of reactive oxygen species via the NADPH oxidase complex. Cíž and Lojek (2013) reviewed the current understanding of how H₁ and H₂ receptors modulate neutrophil oxidative burst and compare this to the newest histamine receptor, the H₄R, where there is growing evidence for involvement. Mast cells are another major immune cell type that combats infection via release of histamine, 5-HT, heparin, eicosanoids and

cytokines into the local interstitium. Histamine dilates post-capillary venules, activates the endothelium and increases blood vessel permeability, resulting in local oedema and the attraction of a range of other inflammatory cells to the site of release. Mast cell stabilizers have clear roles to play in combating this immune response. Finn and Walsh (2013) discussed in detail the modern range of mast cell stabilizers, their mechanisms, and pros and cons. These are based on natural and synthetic strategies. Interestingly, some second generation have dual action effects as mast cell stabilizers and antihistamines, which may underpin an enhanced efficacy. Histamine is a regulator of brain vascular permeability, and both H₁ and H₂ receptors have been previously identified on endothelial cells for a number of years. A study herein has demonstrated for the first time that endothelial cells express the full complement of histamine receptors, most notably H₄ receptors (Karlstedt *et al.*, 2013), which has significant implications for many CNS diseases, including multiple sclerosis (MS) where permeability of brain micro-vessels are key to the chronicity and severity of the disease. A complementary study showed that H₄R has a role to play in controlling the severity of a mouse model of MS (Ballerini *et al.*, 2013). Perhaps, the endothelial expression profile is relevant to this. This current study is consistent with a recent publication with the H₄R knockout mouse model that displays increased disease severity, as seen with the H₄R antagonist. Future work should concentrate on assessing the effects of an H₄R agonist as a potential therapy for MS.

A key topic of robust discussion during the COST Action centred around the concept of agonist-driven differential signalling (G-protein coupled and independent), so-called biased signalling. Herein, an original article has identified using computational analysis and correlating ligand structures (based on 2-aminopyrimidine congeners of the classic H₄R ligand prototype JNJ7777120) with intrinsic activities, efficacy structural hotspots responsible for non-G-protein biased- β -arrestin2 recruitment (Nijmeijer *et al.*, 2013a,b). One JNJ7777120 2-aminopyrimidine derivative was identified as an unbiased ligand, while the majority were shown to be biased towards β -arrestin signalling. A further study from the same group has reported the importance of the hH₄ receptor-C983.36 residue in unbiased signalling using a novel covalent 2-aminopyrimidine agonist ligand, VUF14480 (Nijmeijer *et al.*, 2013b), providing the beginnings of a structural framework for the model proposed.

Chemogenomics is a relatively new discipline that is proving a very powerful tool for medicinal chemists and pharmacologists to understand the ligand binding process. It entails a dual strategy of identifying the links between the chemical structures of biologically active ligands and the protein targets with which these ligands interact. Kooistra *et al.* (2013) provide an enlightening series of analyses using the histamine receptor family as a model system, which can be clearly extrapolated to other aminergic, and perhaps non-aminergic GPCRs. The recent availability of expanding crystal structural information has aided this significant advance.

There is a growing number of H₃R single-point mutations identified to be linked with neurological disorders. One such mutation is an alanine to valine exchange at amino acid position 280 (A280V) in the third intracellular loop of the receptor, first identified in a patient suffering from Shy-

Drager syndrome and later reported as a risk factor for migraine. This mutation reduced H₃R-mediated signalling efficacy (Flores-Clemente *et al.*, 2013); how this correlates with Shy-Drager syndrome is not clear, as such an effect would be predicted to increase noradrenergic function unless this is largely an autoreceptor effect with consequences downstream upon heteroreceptors. The link between reduced efficacy of the mutation and migraine is more understandable, with regard to consequent enhanced glutamate and neuropeptide release.

Important differences between recombinant and native monocyte cell culture studies were described in detail by Gschwandtner *et al.* (2013), who provided further support for the importance of studying H₄R in native cells for improved correlation to preclinical and clinical development. Such a correlation remains problematical and an issue much discussed within COST Action BM0806; H₄R display clear species variation that has forced some pharmaceutical companies to leap immediately to the clinic by-passing preclinical validation and development in *in vitro* and *in vivo* rodent models. Human studies relating imaging and behavioural studies focused on the histamine system are limited in recent times. The effects of betahistine (mixed H₃ antagonist/H₁ agonist) on learning and memory, and associated brain activity were assessed by van Ruitenbeek and Mehta (2013), which adds new information to this limited research arena.

The H₁R anti-histamine class of drugs is the group of choice for the relief of vestibular disorder symptom, particularly vertigo and motion sickness with the medial vestibular nucleus (MVN) of the brain stem believed to be the primary site of action. Notably, Zhang *et al.* (2013) reported new evidence for the histamine H₁ and H₂ receptor acting as potent mediators on the postsynaptic neurons in the MVN. This group reported a lack of H₄R involvement, which is controversial as a recent *British Journal of Pharmacology* publication provided pharmacological evidence for H₄R antagonists producing a pronounced inhibitory effect on vestibular neuron activity (Desmadryl *et al.*, 2012). This issue requires clarification.

The nucleus accumbens (NAc) has long been associated with emotional processes relating to a range of affective and psychotic disorders; the histaminergic system has been recently linked to these clinical needs. Histaminergic neurons synapsing within the NAc stimulates H₁ heteroreceptors, which, in turn, increases spontaneous release of glutamate, aspartate and acetylcholine in the NAc. Furthermore, stimulation of H₁ receptors by endogenous histamine within the NAc accentuates the release of glutamate and ACh in the NAc elicited specifically by stimulation of the hippocampal fornix/fimbria (Kraus *et al.*, 2013). These effects may underpin the pathophysiological benefits of some histaminergic drugs.

There is an intimate association between dopamine and histamine in the striatum with heterodimers of postsynaptic D₂ and H₃R present in high concentration on the medium spiny neurons. The long history of dopamine and addiction suggests a potential regulatory role of histamine (reviewed in Ellenbroek, 2013). The most consistent findings have been reported for ethanol addiction, where H₃ receptor antagonists/inverse agonists have generally been found to reduce ethanol intake. A recent study showed that the novel

H₃ receptor antagonist/inverse agonist JNJ-39220675 inhibits ethanol self-administration in alcohol l-preferring rats, and Vanhanen *et al.* (2013) provided new evidence that the H₃ receptor mediates alcohol reward inhibition but not consumption or stimulation, somewhat confuses the situation.

The group of Professor Elena Rivera has previously reported the presence of H₄R on benign and malignant lesions and cell lines derived from the human mammary gland. The same group reported in this volume that activation of this receptor with a range of agonists, including selective examples, reduced the tumour progression rate *in vitro* and *in vivo*, offering H₄R as an exciting new therapeutic target for breast cancers (Martinel Lamas *et al.*, 2013).

In conclusion, as the EHRS enters its 43rd year, histamine remains one of the richest sources of pharmacological delights, with ever expanding clinical potential. I hope Jim and Walter are proud of our efforts regarding exploiting the histaminergic system and subsequent rational drug design.

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