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EDITORIAL

Advances in histamine pharmacology reveal new drug targets

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This Themed Issue consists of three reviews and 11 original articles authored by internationally respected industrial and academic pharmacologists from across three continents. It derives from the highly successful symposium on 'The H_3 and H_4 histamine receptors: the antihistamines for the 21st century', which took place at EPHAR 2008 in Manchester University, and encompasses new roles, new compounds and exciting new therapeutic areas for histamine.
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Abbreviations: EPHAR, European Pharmacological Societies; ESF COST, European Science Foundation Cooperation in Science and Technology; PET, Positron emission tomography; SPECT, Single photon emission computed tomography

Histamine (2-(imidazol-4-yl) ethylamine) is found in most tissues of the body but is present in high concentrations in the lungs and the skin and in particularly high concentrations in the gastrointestinal tract. It is found mainly in mast cells and basophils, associated with heparin, but non-mast-cell histamine is also present in 'histaminocytes' in the stomach and in histaminergic neurons in the brain. Ever since the seminal studies using histamine by the father of modern-day pharmacology, Sir Henry Dale, in the early 1930s, the histaminergic system has proved to be one of the most productive areas for successful clinical pharmacology, proving a rich source of useful drugs, particularly over the last three decades. Antagonists for the histamine H_1 (fexofenadine in Allegra® or l-cetirizine in Xyzal®) or H_2 receptors (cimetidine in Tagamet® or ranitidine in Zantac®) have both reached blockbuster status and been successfully used for many years in the treatment of allergic conditions and gastric ulcers respectively. Currently, attention in the pharmaceutical industry is directed towards the therapeutic use of the newest members of the histamine receptor family, namely the H_3 and H_4 receptors. Histamine H_3 and H_4 receptor antagonists are currently in preclinical development and in early stages of clinical trials for a range of cognitive, psychotic, sleep and inflammatory disorders, obesity and cancers. A number of internationally renowned industrial and academic pharmacologists from Europe, the US and New Zealand appear in this Themed Issue that arose from the successful symposium 'The H_3 and H_4 histamine receptors: the antihistamines for the 21st century' organized by myself and Dr Katherine Tiligada (University of Athens, Greece) at EPHAR 2008 in Manchester University. It brings together a rich array of review and original articles spanning medicinal chemistry and the molecular, behavioural and clinical pharmacology of histamine. A number of the leading pharmaceutical companies, including GSK, Abbott and Johnson and Johnson, together with academic drug developers from the Netherlands and Spain report in a series of original articles new pharmacological data for novel chemical structural leads for the H_3 and H_4 receptors, together with a review discussing a novel modelling strategy for developing histidine decarboxylase inhibitors as a proof of concept (Moya-García *et al.*, 2009).

The two main reviews within this volume focus on the newest member of the histamine receptor family, namely the H_4 receptor, covering the latest findings relating to its molecular and biochemical pharmacology, from Leurs *et al.* (2009), and exciting roles in the immune system and in inflammation from Zampeli and Tiligada (2009). The histamine H_4 receptor is a highly topical drug target for a growing spectrum of therapeutic areas as evidenced by the recently successful funding of the European ESF COST Action BM0806 entitled 'Histamine H_4 receptor research' (HARR4-EU COST); many of the present authors being Management Committee members of this new action. In an original publication from Lim *et al.* (2009), a new improved selective H_4 receptor agonist is reported, which will prove invaluable in the pharmacological dissection of this highly topical new drug target. A second original article from Strakhova *et al.* (2009) reports the detailed pharmacological properties of a new potent highly

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selective H_4 receptor antagonist, which adds to the range of pharmacophores available to study this histamine receptor. Improved pharmacokinetic properties displayed by this ligand should aid in its potential clinical use for chronic inflammatory disorders. Connelly *et al.* (2009) have provided important new evidence that the H_4 receptor is not exclusively expressed on haematopoietic cells. Here, they report the first pharmacological evidence, using a selective H_4 receptor antagonist, for functional histamine H_4 receptors on cortical neurons. This adds to the growing evidence for the H_4 receptor subtype subserving distinct roles on multiple cell types in the body, which is further elaborated in the review by Leurs *et al.* (2009).

Oligomerization of G protein-coupled receptors (GPCRs) is a mature theme in pharmacology and the GPCRs of the histamine receptor family provide many examples of this phenomenon. As well as previously reported homo-oligomerization, hetero-oligomerization appears to be possible even with different GPCR families. In this volume, Ferrada *et al.* (2009) report evidence for the presence *in vivo* of the heteromeric partners, histamine H_3 and dopamine D_1 receptors, focusing on the issue of signal transactivation, a growing concept in GPCR pharmacology. The clinical relevance of such functional interactions is clear as both receptor families are implicated in a wide spectrum of clinical CNS disorders and diseases.

Manipulating the histaminergic system in the CNS is clearly a validated approach for many clinical indications, but the consequences for cognitive function require continuing attention. Blockade of histamine H_1 receptors has been previously implicated in learning deficits with the first generation anti-histamines. Here, van Ruitenbeek *et al.* (2009a) provide new evidence that hypofunction of the human central histaminergic system (through blockade of the H_1 receptor) reduced sensory, rather than motor information processing, and Zlomuzica *et al.* (2009) report that genetic inactivation of the H_1 receptor in the mouse leads to spatial working and reference memory impairments, while having no significant effect on emotional behaviour in the light–dark test. For the first time, van Ruitenbeek *et al.* (2009b) report the results of a study that decreased histamine levels, by depleting its precursor L-histidine, in human volunteers. This method was then used to study the role of histamine in cognitive performance. Although modest effects upon histamine levels and behavioural outcomes were observed, this clearly forms the basis for an interesting new protocol to study the effects of the depletion of histamine (and other monoamines) in the clinic.

The histamine H_3 receptor is highly expressed in a number of key structures in the mammalian and human CNS, and clearly subserves key modulatory roles, particularly those relating to sleep and feeding behaviours, attention and cognitive processing, as well as specific types of nociception and movement co-ordination (see Vohora, 2008). The growing physiological and pharmacological information has laid the foundation for the recent therapeutic advancement of compounds acting on central H_3 receptors. Narcolepsy is the first indication being assessed for H_3 receptor antagonists in the clinic, with a number of phase I and II trials ongoing. Acute dosing with such compounds has shown beneficial effects (increased wakefulness) in animal models of narcolepsy. In this Issue, Guo *et al.* (2009) provide important new evidence that selective H_3 receptor antagonists (in this case GSK189254) are still effective, even after repeated dosing, using the orexin-knock out mouse model of narcolepsy.

Another important clinical area in which targeting of the histamine H_3 receptor has been pursued is psychotic disorders, particularly related to the cognitive deficits seen in schizophrenia. Jin *et al.* (2009) report new findings that show an elevated level of H_3 receptors in the prefrontal cortex and reduced levels in the hippocampus, which project to many cortical and subcortical regions, which may explain the cognitive deficits seen within this patient group. Medhurst *et al.* (2009) reported the preservation of H_3 receptors in many key brain structures in cases of advanced Alzheimer's disease, but an elevated receptor level again in the prefrontal cortex, which correlated with increased severity of cognitive impairment. These two studies provide further new evidence to validate the use of histamine H_3 receptor antagonists for cognitive dysfunctions in a range of neurological and psychological disorders.

In order to maximize translation from preclinical optimism to clinical success, predictive assessments are vital. Miller *et al.* (2009) reported a useful alternative to current *ex vivo* approaches to measure receptor occupancy, which are fraught with problems, including dissociation of radiotracer during processing and the assay protocol, which reduces their utility. The *in vivo* method to assess receptor occupation described here relies on reduction of radiotracer levels in specific brain regions in comparison with vehicle-treated controls, based on scintillation counting, and is analogous to a PET/SPECT imaging system. Lack of suitable radiotracers to assess H_3 receptor occupancy, because of poor brain penetration and high non-specific binding, has negated the use of this methodology with the older H_3 receptor ligands; interestingly, these older ligands subsequently failed in the clinic. Using a newer, highly selective H_3 receptor radiotracer, the relationship between receptor occupancy and drug doses, blood exposure level and efficacy in behavioural tests could be established, demonstrating general utility of this methodology in preclinical assessment.

Overall, this topical Themed Issue highlights the rapid emergence of the targets for the next generation of anti-histamine drugs, namely the histamine H_3 and H_4 receptors, which hold significant promise in a wide range of clinical areas. The i*n vitro* and *in vivo* pharmacological studies, together with new strategies for drug discovery, reported here confirm that there are exciting times ahead for histamine pharmacology.

References

Connelly WM, Shenton FC, Lethbridge N, Leurs R, Waldvogel HJ, Faull RLM *et al.* (2009). The histamine H_4 receptor is functionally expressed on neurons in the mammalian CNS. *Br J Pharmacol* **157**: 55–63.

Ferrada C, Moreno E, Casadó V, Bongers G, Cortés A, Mallol J *et al.* (2009). Marked changes in signal transduction upon heteromerization of dopamine D_1 and histamine H_3 receptors. *Br J Pharmacol* **157**: 64–75.

Guo RX, Anaclet C, Roberts JC, Parmentier R, Zhang M, Guidon G *et al*. (2009). Differential effects of acute and repeat dosing with the H_3 antagonist GSK189254 on the sleep-wake cycle and narcoleptic episodes in Ox-/- mice. *Br J Pharmacol* **157**: 104–117.

Leurs R, Chazot PL, Shenton FC, Lim H, de Esch IJP (2009). Molecular and biochemical pharmacology of the histamine H_4 receptor. *Br J Pharmacol* **157**: 14–23.

Jin CY, Anichtchik O, Panula P (2009). Altered histamine H_3 receptor radioligand binding in post-mortem brain samples from subjects with psychiatric diseases. *Br J Pharmacol* **157**: 118–129.

Lim HD, Adami M, Guaita E, Werfel T, Smits RA, de Esch IJP *et al*. (2009). Pharmacological characterization of the new histamine H_4 receptor agonist, VUF 8430. *Br J Pharmacol* **157**: 34–43.

Medhurst AD, Roberts JC, Lee J, Chen CPL-H, Brown SH, Roman S *et al*. (2009). Characterization of histamine H_3 receptors in Alzheimer's Disease brain and amyloid over-expressing TASTPM mice. *Br J Pharmacol* **157**: 130–138.

Miller TR, Milicic I, Bauch J, Du J, Surber B, Browman KE *et al*. (2009). Use of the H_3 receptor antagonist radioligand [^{3}H]-A-349821 to reveal *in vivo* receptor occupancy of cognition-enhancing H_3 receptor antagonists. *Br J Pharmacol* **157**: 139–149.

Moya-García AA, Pino-Ángeles A, Gil-Redondo R, Morreale A, Sánchez-Jiménez F (2009). Structural features of mammalian histidine decarboxylase reveal the basis for specific inhibition. *Br J Pharmacol* **157**: 4–13.

van Ruitenbeek P, Vermeeren A, Smulders FTY, Sambeth A, Riedel WJ (2009a). Histamine H_1 receptor blockade predominantly impairs sensory processes in human sensorimotor performance. *Br J Pharmacol* **157**: 76–85.

van Ruitenbeek P, Sambeth A, Vermeeren A, Young SN, Riedel WJ (2009b). Effects of L-histidine depletion and L-tyrosine/L-phenylalanine depletion on sensory and motor processes in healthy volunteers. *Br J Pharmacol* **157**: 92–103.

Strakhova MI, Cuff CA, Manelli AM, Carr TL, Witte DG, Baranowski JL *et al*. (2009). *In vitro* and *in vivo* characterization of A-940894: a potent histamine H4 receptor antagonist with anti-inflammatory properties. *Br J Pharmacol* **157**: 44–54.

Zampeli E, Tiligada E (2009). The role of histamine H_4 receptor in immune and inflammatory disorders. *Br J Pharmacol* **157**: 24–33.

Zlomuzica A, Sadile AG, Huston JP, Dere E (2009). Histamine H_1 receptor knockout mice exhibit impaired spatial memory in the eight-arm radial maze. *Br J Pharmacol* **157**: 86–91.

Vohora D (ed.) (2008) *The Third Histamine Receptor*. CRC Press (Taylor & Francis Group): Boca Raton, FL.