Chapter 2

Molecular Pharmacology of the Four Histamine Receptors

Gerold Bongers, Iwan de Esch and Rob Leurs*

Abstract

Histamine and its receptors have been (and are still today) very fruitful topics for pharmacological and medicinal chemistry studies. In this chapter we review the various selective ligands that are available for the four different histamine receptors and we describe the main molecular pharmacological aspects of each of the receptor subtypes.

The Discovery of the Four Histamine Receptors: An Historical Overview

The biological effects of histamine were observed early by Dale and Laidlaw (1910). Injection of the biogenic amine produced similar effects as in many allergic reactions.[1] As early as 1937, the first evidence for a histamine receptor was provided by Bovet and Staub, who discovered the first antihistamine thymoxidiethylamine, that was capable of preventing anaphylactic shock in animals.[2] The discovery by Ash and Schild in 1966 that antihistamines, like mepyramine, could block certain pharmacological actions of histamine on symptoms of allergic reactions, but not the effects on the gastric acid secretion led the hypothesis that there were at least two subtypes of histamine receptors.[3] This was further corroborated by the finding that burimamide selectively antagonized the histamine mediated effects on the gastric acid secretion.[4] The histamine mediated auto-inhibition of brain histamine release was shown to by mediated by a third class of histamine receptors that could be pharmacologically differentiated from the heretofore known histamine H_1 receptor (H_1R) and histamine H_2 receptor (H_2R).[5] The histamine H_3 receptor (H_3R) was definitely confirmed by the first selective and potent H_3R antagonists thioperamide.[6] The last member of the histamine receptor family was originally cloned as an orphan receptor, but based on its high sequence homology to the H_3R was found to respond to histamine and confirmed to be a fourth histamine receptor, the histamine H_4 receptor (H_4R).[7-11]

The four histamine receptors are all membrane bound proteins that belong to the superfamily of the G-protein coupled receptors (GPCRs) and more precisely to the biogenic amine receptors in the rhodopsin-family. GPCRs convert diverse stimuli like odors, photons, neurotransmitters (including biogenic amines), hormones, peptides and proteases, via guanine nucleotide-binding proteins (G-proteins) into intracellular responses. GPCRs are characterized by seven alpha helical transmembrane (TM) domains and are found in eukaryotes, including yeast, plants, choanoflagellates and animals. They are involved in numerous physiological processes like smell, taste, vision, behavior and mood, regulation of the immune system and autonomic nervous system transmission. GPCRs are considered attractive drug targets by the pharmaceutical industry, because they are involved in the regulation of almost every major mammalian physiological process and are

*Corresponding Author: Rob Leurs—Leiden/Amsterdam Center for Drug Research (LACDR), Division of Medicinal Chemistry, Faculty of Sciences, VU University, Amsterdam, De Boelelaan 1083, 1081 HV, Amsterdam, The Netherlands. Email: leurs@few.vu.nl

Histamine in Inflammation, edited by Robin L. Thurmond.

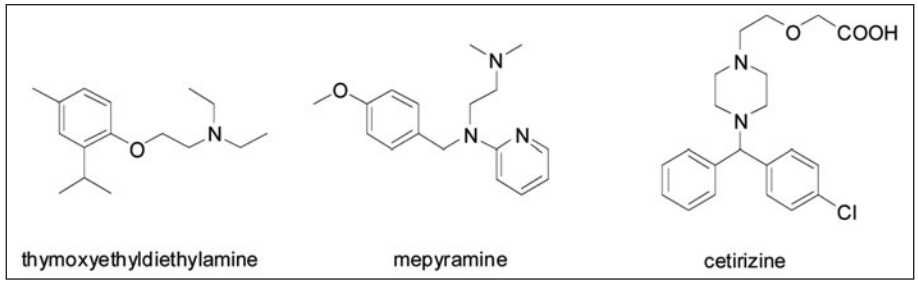

Figure 1. Chemical structures of selected H_1R antagonists.

readily accessible to drugs due to their localization on the cell surface. In fact, 30% of all drugs on the market are targeting GPCRs, among these are several block-buster drugs like clopidogrel (Plavix®), cimetidine (Tagamet®), Fexofenadine hydrochloride (Allegra®), quetiapine (Seroquel®) and metoprolol (Lopressor® or Seloken®).[12,13] Recently, considerable progress has been made in the purification and crystallization of several members of the rhodopsin class of GPCRs,[14-16] likely further enhancing the success of GPCR based drug discovery.

Histamine Receptors, Signal Transduction and Their Ligands

In the next paragraphs we will discuss various molecular pharmacological aspects of the four different receptor subtypes, including the availability of selective subtype selective agonists and antagonists.

The Histamine H_1 Receptor and Its Ligands

The histamine H_1 receptor (H_1R) is found mainly on smooth muscle cells, endothelium and in the CNS. Its physiological role includes e.g., vasodilatation, bronchoconstriction, modulation of endothelial barrier function (responsible for hives), pain and itching due to insect stings. The antagonists for the H_1R, commonly known as antihistamines, are successfully used for the treatment of allergic rhinitis and skin irritations.[17] Following the first antihistamine, thymoxyethyldiethylamine (Fig. 1), the related ethylenediamines (e.g., mepyramine) were the first clinically used H_1R antagonists. Like the other first generation H_1R antagonists, the use of mepyramine however suffers from sedation as a side effect. Actually, these compounds are now used in many sleeping-aid preparations. Second generation antagonists for the H_1R, e.g., the piperazine cetirizine, have a reduced occurrence of adverse drug reactions due to a decreased brain penetration and increased H_1R selectivity.[18]

Some selective H_1R agonists have recently been developed as well, but are not used therapeutically. Modification of the imidazole moiety of histamine has been the most successful approach for obtaining selective H_1 agonists (Fig. 2). The presence of the tautomeric N^{π}-N^{τ} system of the imidazole ring is

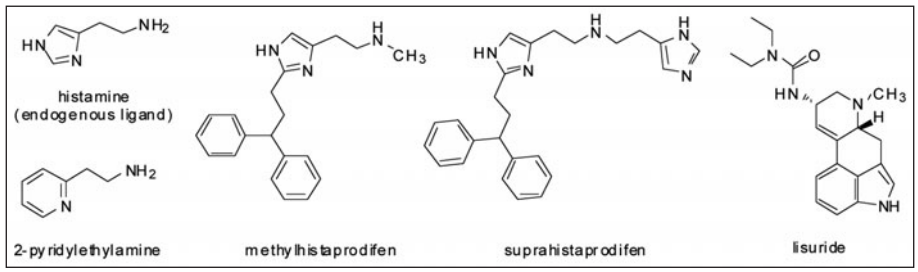

Figure 2. Chemical structures of selected H_1R agonists.

not obligatory, as reflected by the selective, but weak H_1 agonists 2-pyridylethylamine. Substitution of the imidazole ring at the 2-position leads to relatively selective H_1 agonists. Schunack and colleagues developed a series of H_1R selective histaprodifens.[19-21] A further increase in H_1R agonist potency was obtained by a bivalent ligand approach. Suprahistaprodifen, a dimer of histaprodifen and histamine is currently one of the most potent H_1R agonists available.[22,23] Surprisingly, recent high throughput screening of CNS-active drugs at the H_1R has identified the non-imidazole ergot derivative lisuride as another high affinity H_1R agonist.[24]

The bovine H_1R cDNA was cloned from a cDNA library of bovine adrenal medulla and was the first H_1R gene to be cloned,[25] soon to be followed by other species, including the human H_1R.[26-28] The human H_1R gene is an intron-less gene that is located on chromosome 3p25 and encodes for a 487 amino acid GPCR with a long third intracellular loop (IL3).[29]

The H_1R predominantly couples to $G\alpha_{q/11}$-proteins[30] leading to the activation of PLC and subsequent release of the second messengers IP_3 and DAG followed by the activation of PKC and the release of $[Ca^{2+}]_i$. Additionally, the H_1R has been shown to constitutively increase IP_3 levels[31] and to activate the nuclear factor κB (NF-κB),[32] a transcription factor involved in inflammation and cancer. Remarkably, the H_1R-mediated constitutive activation of NF-κB is primarily mediated through G-protein βγ-subunits, whereas both $G\alpha_{q/11}$-proteins and βγ-subunits are required for the H_1R agonists mediated NF-κB activation.[32] All the clinically used H_1R antagonists, in fact act as inverse agonists inhibiting the constitutive activation of the H_1R.

The Histamine H_2 Receptor and Its Ligands

The histamine H_2 receptor (H_2R) is located in a variety of tissues including brain, gastric cells and cardiac tissue.[17] H_2Rs are involved in the gastric acid secretion and therefore antagonists of the H_2R are used in the treatment of peptic ulcers. The first H_2R antagonist, burimamide (Fig. 3),[4] was not very potent and actually was not very specific for the H_2R either. With the discovery of the H_3R and H_4R we now know that burimamide has a higher affinity for the H_3R and H_4R.[5,33] Further development within the class of H_2R antagonists led to the discovery of cimetidine (Tagamet®) by Smith, Kline and French and ranitidine (Zantac®) by GlaxoSmithKline. These H_2R antagonists have been widely used in the clinical treatment of peptic ulcers and have become major blockbusters. Nowadays it has become apparent that gastric ulcers can effectively be cured by a proton-pump inhibitor in combination with antibiotics when an infection with *H. pylori* is found.[34-36]

A first step towards a selective H_2R agonist was made with the discovery of dimaprit (Fig. 4), which was found in a quest for isothiourea-based H_2R antagonists. Dimaprit is an H_2R agonist that is almost as active as histamine at the H_2R, but hardly displays any H_1R agonism. Later it was found that dimaprit is also a moderate H_3R antagonist and a moderate H_4R agonist. Using dimaprit as a template, amthamine (2-amino-5-(2-aminoethyl)-4-methylthiazole) was designed as a rigid dimaprit analogue (Fig. 4).[37] Amthamine combines a high H_2R selectivity with a potency, which is slightly higher compared to histamine, both in vitro and in vivo.

The H_2R gene was the first gene of the histamine receptor family to be cloned. By using degenerate oligonucleotide primers based on the known homology between GPCRs and subsequent polymerase chain reaction (PCR) on canine gastric parietal cell cDNA Gantz and coworkers cloned the canine H_2R.[38] High homology of the various H_2R facilitated cloning of the H_2R in other species, including the human H_2R gene.[39] The human H_2R gene is an intron-less gene

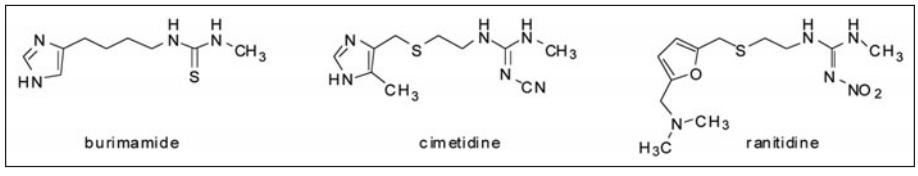

Figure 3. Chemical structures of H_2R antagonists.

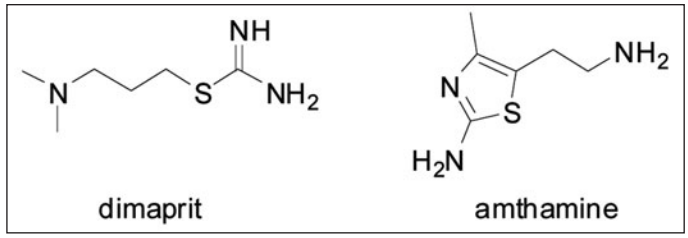

Figure 4. Chemical structures of H_2R agonists.

located on chromosome 5q35 encoding for a protein of 358 amino acids. Compared to the other histamine receptors the H_2R has a short IL3 and a longer C-terminal tail. The H_2R predominantly couples to $G\alpha_s$-proteins and subsequently leads an increase in intracellular cAMP and the activation PKA. Selective immunoprecipitation of activated G proteins labeled with [α-^{32}P]GTP azidoanilide revealed, in addition to $G\alpha_s$-protein coupling, specific coupling to $G\alpha_q$-proteins as well. Stimulation of recombinantly expressed H_2R in COS-7 cells indeed resulted in an increase in intracellular inositol 3-phosphate (IP_3) and as well as an increase in cAMP.[40] Similar to the H_1R, the H_2R was found to display constitutive activity as well,[41] which led to the reclassification of heretofore known (and clinically important) antagonists (like cimetidine and ranitidine) as inverse agonists. Burimamide was found to be neutral antagonist for the rat H_2R,[41] but acts as a weak partial agonist on the human H_2R.[42]

The Histamine H_3 Receptor and Its Ligands

The histamine H_3 receptor (H_3R) is predominantly expressed in the CNS and to a lesser extent in the peripheral nervous system.[17] On histaminergic neurons in the CNS the H_3R acts as an presynaptic autoreceptor inhibiting the release and synthesis of histamine.[5] On nonhistaminergic neurons in mammalian brain, the H_3R functions as a heteroreceptor inhibiting the release of various important neurotransmitters like serotonin, noradrenalin, acetylcholine and dopamine.[17] Besides neuronal expression, peripheral inhibitory effects of H_3R activation on neurotransmission have been shown to occur in the cardiovascular system, gastrointestinal tract and the airways.[43-46]

The H_3R has been an attractive drug target for both academia and the pharmaceutical industry.[47-51] The H_3R is expressed in brain regions that are critical for cognition (cortex and hippocampus), sleep and homeostatic regulation (hypothalamus).[52] Moreover, the H_3R acts as a heteroreceptor modulating the release of several important neurotransmitters that are involved in processes like cognition, mood and sensory gating.[53-55] In addition, the H_3R acts as an autoreceptor regulating the release and synthesis of histamine, a neurotransmitter that plays a role in vigilance, attention, impulsivity and feeding/weight regulation.[17,56] Therefore, antagonists for the H_3R are currently under investigation in several therapeutic areas including sleep disorders, energy homeostasis and cognitive disorders.[57,58]

The first potent H_3R ligands, e.g., thioperamide and clobenpropit (Fig. 5)[6,59] were based on the structure of histamine and therefore imidazole-based. However, development of H_3R specific antagonists by pharmaceutical companies like GlaxoSmithKline (e.g., GSK-189254), Abbott (e.g., A-423579), Johnson and Johnson, Schering-Plough, Pfizer, UCB Pharma, Merck, Banyu, Eli Lilly, Sanofi-Synthelabo and Roche focused on non-imidazole compounds,[57,60] in order to limit potential drug-drug interactions via the interaction with the cytochrome P450 isoenzymes.[61,62]

At the H_3 receptor, histamine itself is a highly active agonist. Methylation of the α-carbon atom of histamine's ethylamine sidechain leads to R-α-methylhistamine, with a highly reduced activity at both the H_1R—and H_2R and potent agonist activity at the H_3R.[63] For potent H_3 agonism, the amine function of histamine can be incorporated in ring structures. For example, immepip (Fig. 6) is a potent H_3 agonist that is effective in vitro and in vivo. Although

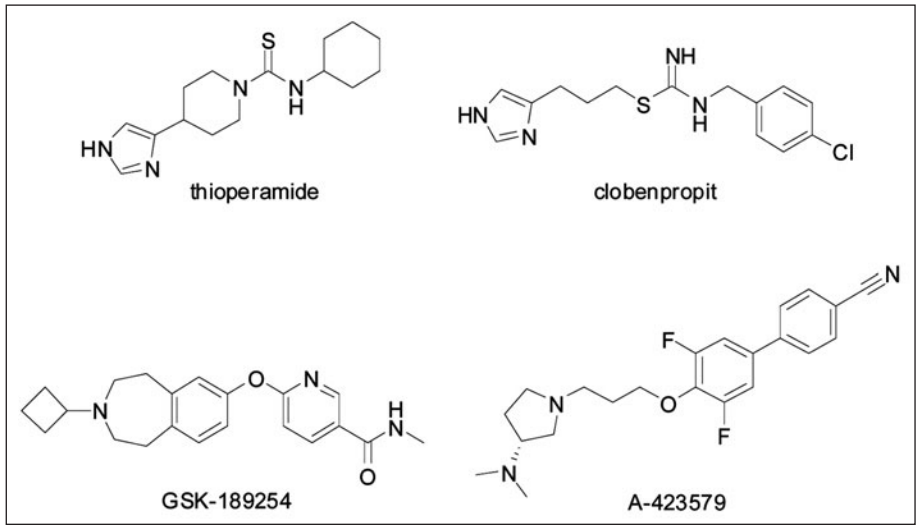

Figure 5. Chemical structures of H_3R antagonists.

immepip and R-α-methylhistamine have previously been used as reference ligands to study the H_3R, both of them have considerable activity for the recently discovered H_4R. Therefore, new potent and selective H_3R agonists have been developed, most notably immethridine (pEC_{50} = 9.8; 300 fold selectivity over the H_4R) and methimepip (pEC_{50} = 9.5; >10000 fold selectivity over the H_4R).[64]

It was not until the turn of last century before the human H_3R cDNA was identified by Lovenberg and his coworkers at Johnson and Johnson in 1999.[65] Earlier efforts to clone the H_3R gene by homology screening on the basis of the earlier elucidated H_1R and H_2R genes all failed. In search for novel GPCRs in commercial genome databases, an orphan GPCR with homology to the M_2 muscarinic acetylcholine receptor was identified. Full pharmacological characterization of this new aminergic GPCR identified this protein as the histamine H_3R. Cloning of the H_3R genes of other species, including rat, guinea pig and mouse, soon followed and important H_3 receptor species differences have been identified.[66] The H_3R mRNA undergoes extensive alternative splicing, resulting in many H_3 receptor isoforms that have different signaling properties and expression profiles.[50,67] Moreover, the H_3R displays particularly high constitutive activity, which can also be observed in vivo, leading to a reclassification of existing ligands into agonists, neutral antagonists and inverse agonists.

The H_3R signals via $G\alpha_{i/o}$ proteins as shown by the pertussis toxin sensitive stimulation of [^{35}S]-GTPγS binding in rat cortical membranes.[68] The inhibition of adenylyl cyclase after stimulation of the H_3R results in lowering of cellular cAMP levels and modulation of CREB (cAMP responsive element-binding protein) dependent gene transcription.[69-75] Moreover, the H_3R effectively couples to the stimulation of MAPK [67] and the Akt-GSK3-β axis.[76]

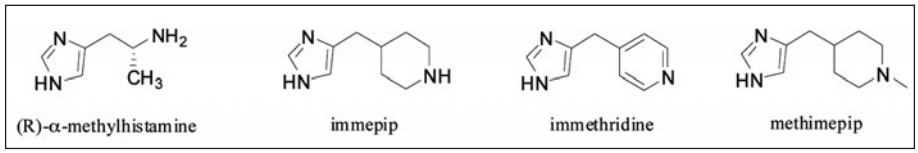

Figure 6. Chemical structures of H_3R agonists.

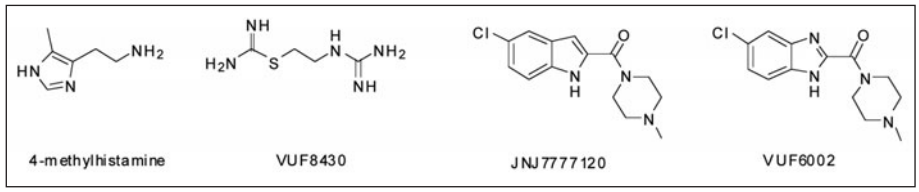

Figure 7. Chemical structures of H_4R ligands.

The Histamine H_4 Receptor and Its Ligands

The histamine H_4 receptor (H_4R) has a relatively low CNS expression and is highly expressed in peripheral blood leukocytes and mast cells, suggesting a role for the H_4R in inflammatory and immune responses.[77] At this moment lot of interest is focused on the potential of the H_4R as drug target in inflammatory conditions (e.g., allergic asthma) and itch. With the discovery of the H_4R and its initial pharmacological characterization,[7-11] it became immediately clear that many imidazole-containing H_3R ligands show a high affinity for the H_4R as well.[78] This is probably due to the high homology (68%) in the transmembrane regions of the H_3R and H_4R.[8,9,33,79] Classical H_3R ligands like the H_3R agonists immepip and imetit and the H_3R inverse agonist clobenpropit were shown to be potent high affinity agonists on the H_4R,[78] whereas thioperamide turns out to be a high affinity inverse agonist for the H_4R.[33] The first potent and H_4R selective agonists, 4-methylhistamine[80] and VUF8430[78] and inverse agonists, JNJ 7777120[81] and its benzimidazole derivative VUF600[2,82,83] have now been developed (Fig. 7). These specific H_4R ligands, together with the availability of H_3R specific ligands,[84] will help to delineate the roles of the H_4R in vivo.

The gene that encodes for the human H_4R is located on chromosome 18q11.2 and contains three exons encoding for a 390 amino acid protein that has a 31% homology to the human H_3R.[85] Similarity in gene organization between the H_3R and the H_4R might indicate the possibility of H_4R isoforms, however so far no 7-TM H_4R isoforms have been published.[7,9,11,86] Like the H_3R, the H_4R couples to $G\alpha_{i/o}$-proteins, subsequently leading to an inhibition of cAMP accumulation and the subsequent PKA dependent inhibition of the cAMP responsive element-binding protein (CREB).[10] Furthermore, activation H_4R has been shown to lead to a $G\alpha_{i/o}$-protein dependent phosphorylation of MAPK in HEK293 cells[87,88] and mobilization of $[Ca^{2+}]_i$ in mast cells endogenously expressing the H_4R and in L1.2 cells that recombinantly express the H_4R.[87] The H_4R mediated mobilization of $[Ca^{2+}]_i$ in mast cells is both $G\alpha_{i/o}$-protein and PLC dependent as shown by the use of PTX and the phospholipase C inhibitor U73122.[65]

Conclusion

After the first successful period of histamine receptor pharmacology and the blockbuster success of the histamine H_1R and H_2R antagonists, the histamine research area is now having a firm revival. With the cloning of the genes of the H_3R and H_4R worldwide significant attention is paid to the potential therapeutic use of ligands acting at these two "new" family members. It is anticipated that in the coming years the first clinical results with recently developed H_3R and H_4R antagonists will be made public.

References

1. Dale HH, Laidlaw PP. J Physiol 1910; 41:318-344.
2. Bovet D, Staub AM. Comp rend Soc Biol 1937; (124):547.
3. Ash AS, Schild HO. Receptors mediating some actions of histamine. Br J Pharmacol Chemother 1966; 27(2):427-439.
4. Black JW, Duncan WA, Durant CJ et al. Definition and antagonism of histamine H_2-receptors. Nature 1972; 236(5347):385-390.
5. Arrang JM, Garbarg M, Schwartz JC. Auto-inhibition of brain histamine release mediated by a novel class (H_3) of histamine receptor. Nature 1983; 302(5911):832-837.

6. Arrang JM, Garbarg M, Lancelot JC et al. Highly potent and selective ligands for histamine H_3-receptors. Nature 1987; 327(6118):117-123.
7. Zhu Y, Michalovich D, Wu H et al. Cloning, expression and pharmacological characterization of a novel human histamine receptor. Mol Pharmacol 2001; 59(3):434-441.
8. Nguyen T, Shapiro DA, George SR et al. Discovery of a novel member of the histamine receptor family. Mol Pharmacol 2001; 59(3):427-433.
9. Liu C, Ma X, Jiang X et al. Cloning and pharmacological characterization of a fourth histamine receptor (H(4)) expressed in bone marrow. Mol Pharmacol 2001; 59(3):420-426.
10. Morse KL, Behan J, Laz TM et al. Cloning and characterization of a novel human histamine receptor. J Pharmacol Exp Ther 2001; 296(3):1058-1066.
11. Oda T, Morikawa N, Saito Y et al. Molecular cloning and characterization of a novel type of histamine receptor preferentially expressed in leukocytes. J Biol Chem 2000; 275(47):36781-36786.
12. Wise A, Gearing K, Rees S. Target validation of G-protein coupled receptors. Drug Discov Today 2002; 7(4):235-246.
13. Service RF. Surviving the blockbuster syndrome. Science 2004; 303(5665):1796-1799.
14. Cherezov V, Rosenbaum D, Hanson MA et al. High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. Science 2007; 318(5854):1258-1265.
15. Rosenbaum D, Cherezov V, Hanson MA et al. GPCR engineering yields high-resolution structural insights into beta2-adrenergic receptor function. Science 2007; 318(5854):1266-1273.
16. Rasmussen S, Choi H, Rosenbaum D et al. Crystal structure of the human beta2 adrenergic G-protein-coupled receptor. Nature 2007; 450(7168):383-387.
17. Hill SJ, Ganellin CR, Timmerman H et al. International Union of Pharmacology. XIII. Classification of histamine receptors. Pharmacol Rev 1997; 49(3):253-278.
18. Kay GG. The effects of antihistamines on cognition and performance. J Allergy Clin Immunol 2000; 105(6 Pt 2):S622-S627.
19. Elz S, Kramer K, Leschke C et al. Ring-substituted histaprodifen analogues as partial agonists for histamine $H_{(1)}$ receptors: synthesis and structure-activity relationships. Eur J Med Chem 2000; 35(1):41-52.
20. Elz S, Kramer K, Pertz HH et al. Histaprodifens: synthesis, pharmacological in vitro evaluation and molecular modeling of a new class of highly active and selective histamine $H_{(1)}$-receptor agonists. J Med Chem 2000; 43(6):1071-1084.
21. Malinowska B, Piszcz J, Schlicker E et al. Histaprodifen, methylhistaprodifen and dimethylhistaprodifen are potent H_1-receptor agonists in the pithed and in the anaesthetized rat. Naunyn Schmiedebergs Arch Pharmacol 1999; 359(1):11-16.
22. Menghin S, Pertz HH, Kramer K et al. N(alpha)-imidazolylalkyl and pyridylalkyl derivatives of histaprodifen: synthesis and in vitro evaluation of highly potent histamine $H_{(1)}$-receptor agonists. J Med Chem 2003; 46(25):5458-5470.
23. Čarman-Kržan M, Bavec A, Zorko M et al. Molecular characterization of specific H_1-receptor agonists histaprodifen and its Nα-substituted analogues on bovine aortic H_1-receptors. Naunyn Schmiedebergs Arch Pharmacol 2003; 367(5):538-546.
24. Bakker RA, Weiner DM, ter Laak T et al. 8R-lisuride is a potent stereospecific histamine H_1-receptor partial agonist. Mol Pharmacol 2004; 65(3):538-549.
25. Yamashita M, Fukui H, Sugama K et al. Expression cloning of a cDNA encoding the bovine histamine H_1 receptor. Proc Natl Acad Sci U S A 1991; 88(24):11515-11519.
26. De Backer MD, Gommeren W, Moereels H et al. Genomic cloning, heterologous expression and pharmacological characterization of a human histamine H_1 receptor. Biochem Biophys Res Commun 1993; 197(3):1601-1608.
27. Fukui H, Fujimoto K, Mizuguchi H et al. Molecular cloning of the human histamine H_1 receptor gene. Biochem Biophys Res Commun 1994; 201(2):894-901.
28. Moguilevsky N, Varsalona F, Noyer M et al. Stable expression of human H_1-histamine-receptor cDNA in Chinese hamster ovary cells. Pharmacological characterisation of the protein, tissue distribution of messenger RNA and chromosomal localisation of the gene. Eur J Biochem/FEBS 1994; 224(2):489-495.
29. De Backer MD, Loonen I, Verhasselt P et al. Structure of the human histamine H_1 receptor gene. Biochem J 1998; 335(Pt 3):663-670.
30. Leopoldt D, Harteneck C, Nurnberg B. G proteins endogenously expressed in Sf 9 cells: interactions with mammalian histamine receptors. Naunyn Schmiedebergs Arch Pharmacol 1997; 356(2):216-224.
31. Bakker RA, Wieland K, Timmerman H et al. Constitutive activity of the histamine $H_{(1)}$ receptor reveals inverse agonism of histamine $H_{(1)}$ receptor antagonists. Eur J Pharmacol 2000; 387(1):R5-R7.
32. Bakker RA, Schoonus SB, Smit MJ et al. Histamine $H_{(1)}$-receptor activation of nuclear factor-kappa B: roles for G beta gamma- and G alpha(q/11)-subunits in constitutive and agonist-mediated signaling. Mol Pharmacol 2001; 60(5):1133-1142.

33. Lim HD, van Rijn RM, Ling P et al. Evaluation of histamine H_1-, H_2- and H_3-receptor ligands at the human histamine H_4 receptor: identification of 4-methylhistamine as the first potent and selective H_4 receptor agonist. J Pharmacol Exp Ther 2005; 314(3):1310-1321.
34. Deakin M, Williams JG. Histamine H_2-receptor antagonists in peptic ulcer disease. Efficacy in healing peptic ulcers. Drugs 1992; 44(5):709-719.
35. Freston JW. Management of peptic ulcers: emerging issues. World J Surg 2000; 24(3):250-255.
36. Penston JG. Review article: clinical aspects of Helicobacter pylori eradication therapy in peptic ulcer disease. Aliment Pharmacol Ther 1996; 10(4):469-486.
37. Eriks JC, van der Goot H, Sterk GJ et al. Histamine H_2-receptor agonists. Synthesis, in vitro pharmacology and qualitative structure-activity relationships of substituted 4- and 5-(2-aminoethyl)thiazoles. J Med Chem 1992; 35(17):3239-3246.
38. Gantz I, Schaffer M, DelValle J et al. Molecular cloning of a gene encoding the histamine H_2 receptor. Proc Natl Acad Sci U S A 1991; 88(2):429-433.
39. Gantz I, Munzert G, Tashiro T et al. Molecular cloning of the human histamine H_2 receptor. Biochem Biophys Res Commun 1991; 178(3):1386-1392.
40. Kuhn B, Schmid A, Harteneck C et al. G proteins of the Gq family couple the H_2 histamine receptor to phospholipase C. Mol Endocrinol 1996; 10(12):1697-1707.
41. Smit MJ, Leurs R, Alewijnse AE et al. Inverse agonism of histamine H_2 antagonist accounts for upregulation of spontaneously active histamine H_2 receptors. Proc Natl Acad Sci U S A 1996; 93(13):6802-6807.
42. Alewijnse AE, Smit MJ, Hoffmann M et al. Constitutive activity and structural instability of the wild-type human H_2 receptor. J Neurochem 1998; 71(2):799-807.
43. Schwartz JC, Arrang JM, Garbarg M et al. Plenary lecture. A third histamine receptor subtype: characterisation, localisation and functions of the H_3-receptor. Agents Actions 1990; 30(1-2):13-23.
44. Bertaccini G, Coruzzi G. An update on histamine H_3 receptors and gastrointestinal functions. Dig Dis Sci 1995; 40(9):2052-2063.
45. Malinowska B, Godlewski G, Schlicker E. Histamine H_3 receptors—general characterization and their function in the cardiovascular system. J Physiol Pharmacol 1998; 49(2):191-211.
46. Delaunois A, Gustin P, Garbarg M et al. Modulation of acetylcholine, capsaicin and substance P effects by histamine H_3 receptors in isolated perfused rabbit lungs. Eur J Pharmacol 1995; 277(2-3):243-250.
47. Alguacil LF, Perez-Garcia C. Histamine H_3 receptor: a potential drug target for the treatment of central nervous system disorders. Curr Drug Targets 2003; 2(5):303-313.
48. Bonaventure P, Letavic M, Dugovic C et al. Histamine H_3 receptor antagonists: from target identification to drug leads. Biochem Pharmacol 2007; 73(8):1084-1096.
49. Hancock AA. The challenge of drug discovery of a GPCR target: analysis of preclinical pharmacology of histamine H_3 antagonists/inverse agonists. Biochem Pharmacol 2006; 71(8):1103-1113.
50. Leurs R, Bakker RA, Timmerman H et al. The histamine H_3 receptor: from gene cloning to H_3 receptor drugs. Nat Rev Drug Discov 2005; 4(2):107-120.
51. Leurs R, Timmerman H. The histamine H_3-receptor: a target for developing new drugs. Progress in drug research. Fortschr Arzneimittelforsch 1992; 39:127-165.
52. Hancock AA, Fox GB. Perspectives on cognitive domains, H_3 receptor ligands and neurological disease. Expert Opin Investig Drugs 2004; 13(10):1237-1248.
53. Caulfield MP, Birdsall NJ. International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. Pharmacol Rev 1998; 50(2):279-290.
54. Missale C, Nash SR, Robinson SW et al. Dopamine receptors: from structure to function. Physiol Rev 1998; 78(1):189-225.
55. Schlicker E, Malinowska B, Kathmann M et al. Modulation of neurotransmitter release via histamine H_3 heteroreceptors. Fundam Clin Pharmacol 1994; 8(2):128-137.
56. Schwartz JC, Arrang JM, Garbarg M et al. Histaminergic transmission in the mammalian brain. Physiol Rev 1991; 71(1):1-51.
57. Wijtmans M, Leurs R, de Esch I. Histamine H_3 receptor ligands break ground in a remarkable plethora of therapeutic areas. Expert Opin Investig Drugs 2007; 16(7):967-985.
58. Passani MB, Lin JS, Hancock A et al. The histamine H_3 receptor as a novel therapeutic target for cognitive and sleep disorders. Trends Pharmacol Sci 2004; 25(12):618-625.
59. van der Goot H, Schepers MJP, Sterk GJ et al. Isothiourea analogues of histamine as potent agonists or antagonists of the histamine H_3-receptor. Eur J Med Chem 1992; 27(5):511-517.
60. Cowart M, Altenbach R, Black L et al. Medicinal chemistry and biological properties of non-imidazole histamine H_3 antagonists. Mini Rev Med Chem 2004; 4(9):979-992.
61. LaBella FS, Queen G, Glavin G et al. H_3 receptor antagonist, thioperamide, inhibits adrenal steroidogenesis and histamine binding to adrenocortical microsomes and binds to cytochrome P450. Br J Pharmacol 1992; 107(1):161-164.

62. Yang R, Hey JA, Aslanian R et al. Coordination of histamine H_3 receptor antagonists with human adrenal cytochrome P450 enzymes. Pharmacology 2002; 66(3):128-135.
63. Arrang JM, Garbarg M, Lancelot JC et al. Highly potent and selective ligands for a new class H_3 of histamine receptor. Invest Radiol 1988; 23 Suppl 1:S130-S132.
64. Kitbunnadaj R, Zuiderveld OP, Christophe B et al. Identification of 4-(1H-imidazol-4(5)-ylmethyl) pyridine (immethridine) as a novel, potent and highly selective histamine $H_{(3)}$ receptor agonist. J Med Chem 2004; 47(10):2414-2417.
65. Lovenberg TW, Roland BL, Wilson SJ et al. Cloning and functional expression of the human histamine H_3 receptor. Mol Pharmacol 1999; 55(6):1101-1107.
66. Hancock AA, Esbenshade TA, Krueger KM et al. Genetic and pharmacological aspects of histamine H_3 receptor heterogeneity. Life Sci 2003; 73(24):3043-3072.
67. Drutel G, Peitsaro N, Karlstedt K et al. Identification of rat H_3 receptor isoforms with different brain expression and signaling properties. Mol Pharmacol 2001; 59(1):1-8.
68. Clark EA, Hill SJ. Sensitivity of histamine H_3 receptor agonist-stimulated [35S]GTP gamma[S] binding to pertussis toxin. Eur J Pharmacol 1996; 296(2):223-225.
69. Wieland K, Bongers G, Yamamoto Y et al. Constitutive activity of histamine $H_{(3)}$ receptors stably expressed in SK-N-MC cells: display of agonism and inverse agonism by $H_{(3)}$ antagonists. J Pharmacol Exp Ther 2001; 299(3):908-914.
70. Morisset S, Rouleau A, Ligneau X et al. High constitutive activity of native H_3 receptors regulates histamine neurons in brain. Nature 2000; 408(6814):860-864.
71. Uveges AJ, Kowal D, Zhang Y et al. The role of transmembrane helix 5 in agonist binding to the human H_3 receptor. J Pharmacol Exp Ther 2002; 301(2):451-458.
72. Cogé F, Guenin SP, Audinot V et al. Genomic organization and characterization of splice variants of the human histamine H_3 receptor. Biochem J 2001; 355(Pt 2):279-288.
73. Gomez-Ramirez J, Ortiz J, Blanco I. Presynaptic H_3 autoreceptors modulate histamine synthesis through cAMP pathway. Mol Pharmacol 2002; 61(1):239-245.
74. Sanchez-Lemus E, Arias-Montano JA. Histamine H_3 receptor activation inhibits dopamine D1 receptor-induced cAMP accumulation in rat striatal slices. Neurosci Lett 2004; 364(3):179-184.
75. Bakker RA, Lozada AF, van Marle A et al. Discovery of naturally occurring splice variants of the rat histamine H_3 receptor that act as dominant-negative isoforms. Mol Pharmacol 2006; 69(4):1194-1206.
76. Bongers G, Sallmen T, Passani MB et al. The Akt/GSK-3beta axis as a new signaling pathway of the histamine H(3) receptor. J Neurochem 2007; 103(1):248-258.
77. Thurmond RL, Gelfand EW, Dunford PJ. The role of histamine H_1 and H_4 receptors in allergic inflammation: the search for new antihistamines. Nat Rev Drug Discov 2008; 7(1):41-53.
78. Jablonowski JA, Grice CA, Chai W et al. The first potent and selective non-imidazole human histamine H_4 receptor antagonists. J Med Chem 2003; 46(19):3957-3960.
79. Liu C, Wilson SJ, Kuei C et al. Comparison of human, mouse, rat and guinea pig histamine H_4 receptors reveals substantial pharmacological species variation. J Pharmacol Exp Ther 2001; 299(1):121-130.
80. Lim HD, Smits RA, Bakker RA et al. Discovery of S-(2-guanidylethyl)-isothiourea (VUF 8430) as a potent nonimidazole histamine H_4 receptor agonist. J Med Chem 2006; 49(23):6650-6651.
81. Thurmond RL, Desai PJ, Dunford PJ et al. A potent and selective histamine H_4 receptor antagonist with anti-inflammatory properties. J Pharmacol Exp Ther Apr 2004; 309(1):404-413.
82. Coruzzi G, Adami M, Guaita E et al. Anti-inflammatory and antinociceptive effects of the selective histamine H_4-receptor antagonists JNJ7777120 and VUF6002 in a rat model of carrageenan-induced acute inflammation. Eur J Pharmacol 2007; 563(1-3):240-244.
83. Zhang M, Thurmond RL, Dunford PJ. The histamine $H_{(4)}$ receptor: a novel modulator of inflammatory and immune disorders. Pharmacol Ther 2007; 113(3):594-606.
84. de Esch IJ, Thurmond RL, Jongejan A et al. The histamine H_4 receptor as a new therapeutic target for inflammation. Trends Pharmacol Sci 2005; 26(9):462-469.
85. Coge F, Guenin SP, Rique H et al. Structure and expression of the human histamine H_4-receptor gene. Biochem Biophys Res Commun 2001; 284(2):301-309.
86. Nakamura T, Itadani H, Hidaka Y et al. Molecular cloning and characterization of a new human histamine receptor, HH_4R. Biochem Biophys Res Commun 2000; 279(2):615-620.
87. Hofstra CL, Desai PJ, Thurmond RL et al. Histamine H_4 receptor mediates chemotaxis and calcium mobilization of mast cells. J Pharmacol Exp Ther 2003; 305(3):1212-1221.
88. Nakayama T, Kato Y, Hieshima K et al. Liver-expressed chemokine/CC chemokine ligand 16 attracts eosinophils by interacting with histamine H_4 receptor. J Immunol 2004; 173(3):2078-2083.