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This review is dedicated to the memory of Professor Sir James Black, FRS, Nobel laureate, who died on 22 March 2010, and Professor Walter Schunack, who died on 6 April 2011.

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Abstract—Histamine is a developmentally highly conserved autacoid found in most vertebrate tissues. Its physiological functions are mediated by four 7-transmembrane G protein-coupled receptors (H₁R, H₂R, H₃R, H₄R) that are all targets of pharmacological intervention. The receptors display molecular heterogeneity and constitutive activity. H₁R antagonists are long known antiallergic and sedating drugs, whereas the H₂R was identified in the 1970s and led to the development

of H₂R-antagonists that revolutionized stomach ulcer treatment. The crystal structure of ligand-bound H₁R has rendered it possible to design new ligands with novel properties. The H₃R is an autoreceptor and heteroreceptor providing negative feedback on histaminergic and inhibition on other neurons. A block of these actions promotes waking. The H₄R occurs on immunocompetent cells and the development of anti-inflammatory drugs is anticipated.

I. Introduction and Historical Perspective

Histamine pharmacology has experienced a renaissance over the last few decades, with the identification and cloning of the histamine H₃ and H₄ receptors, which doubles the members of the histamine receptor family. This has led to a massive increase in our understanding of the histamine systems in the whole body and recently resulted in the introduction of H₃ receptor and H₄ receptor drug leads into late-stage clinical development, with an ever expanding range of potential therapeutic applications. The molecular identification of the H₃ receptor and H₄ receptor, their attendant isoforms, and species variants have now clarified to some degree the pharmacological heterogeneity reported in the 1990s, reviewed in the previous *Pharmacological Reviews* article by Hill et al. (1997). This present review is dedicated to two of the foremost histamine receptor pharmacologists, Sir James Black and Walter Schunack, who sadly died at the beginning of 2010 and 2011, respectively. They provided the field with prototypical compounds and drugs, particularly in the H₂ receptor and H₃ receptor fields and contributed profoundly to our current understanding of histamine pharmacology.

Histamine (1) is an endogenous biogenic amine distributed ubiquitously in the body being present in high concentrations in the lungs, skin, and gastrointestinal tract (Fig. 1). Histamine is synthesized and stored at high concentrations within granules in so called "professional" cells, basophils and mast cells, where it is associated with heparin. Based on a sensitive high-performance liquid chromatography-mass spectrometry method, nonmast cell histamine occurs at high concentrations in enterchromaffin-like cells in the stomach, lymph nodes, and thymus, with modest levels in the liver, lung, and in varicosities of the histaminergic neurons in the brain (Zimmermann et al., 2011). Histamine acts as a neurotransmitter in the nervous system and as a local mediator in the gut, skin, and immune system. Histamine brings about complex physiologic changes, including neurotransmission, inflammation, smooth muscle contraction, dilatation of capillaries, chemotaxis, cytokine production, and gastric acid secretion. These biologic changes occur via four G protein-coupled receptor (GPCR) subtypes: H₁ receptor, H₂ receptor, H₃ receptor, and H₄ receptor. These seven-transmembrane domain GPCR proteins represent the largest family of membrane proteins in

ABBREVIATIONS: bp, base pair; CNS, central nervous system; EAE, experimental autoimmune encephalitis; ECL, extracellular loop; ERK, extracellular signal-regulated kinase; GPCR, G protein-coupled receptor; HDC, histidine decarboxylase; IFN, interferon; IL, interleukin; IPSP, inhibitory postsynaptic potential; KO, knockout; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NAADP, nicotinic acid adenine dinucleotide phosphate; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; PBMC, peripheral blood mononuclear cells; PET, positron emission tomography; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; SAR, structure-activity relationship; TLR, Toll-like receptor; TM, transmembrane; TNF α , tumor necrosis factor α .

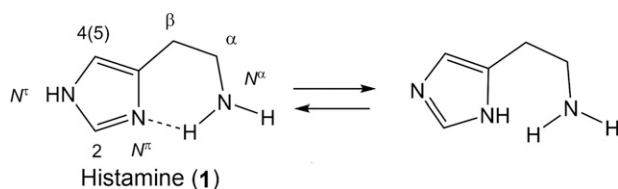


Fig. 1. Histamine.

the human genome (Jacoby et al., 2006; Lagerstrom and Schiöth, 2008) and have proven to be one of the most rewarding families of drug targets to date. All members, including the histamine receptors, share a common membrane topology, comprising an extracellular N terminus, an intracellular C terminus, and seven transmembrane (TM) helices interconnected by three intracellular loops and three extracellular loops. The relative concentrations of histamine required to activate respective histamine receptor subtypes are different. For example, H_1 receptors and H_2 receptors have relatively low affinity for histamine in comparison with H_3 receptors and H_4 receptors, thus the local concentrations of histamine and the presence of different receptor subtypes adds specificity to histamine responses.

The classification of the histamine receptor family was historically based on pharmacological definitions but has subsequently relied upon the molecular biologic identification of new histamine receptor genes and the elucidation of four distinct histamine receptor polypeptide sequences. However, apparent molecular heterogeneity, through alternative splicing, has increased the number of potential receptor isoforms, particularly with the rat and human H_3 receptor. This heterogeneity will be discussed in detail within this review. Moreover, with the availability of recombinant expression systems, new phenomena, including constitutive histamine receptor signaling and receptor oligomerization, have been shown for almost all of the histamine receptor subtypes (see next sections).

Constitutive GPCR activity is recognized for many GPCR family members and results in GPCR signaling without the need of an external agonist (Smit et al., 2007). This spontaneous GPCR signaling is thought to evolve from the conformational dynamics of GPCR proteins, resulting in equilibria between active and inactive receptor states. These equilibria can be altered by GPCR mutations, such as, e.g., in some inherited diseases (Smit et al., 2007), and by GPCR ligands. Agonists drive the equilibria toward active GPCR conformation(s), whereas so-called inverse agonists would favor the inactive conformations. Following this notion, many of the known GPCR antagonists (including the histamine receptor antagonists) have been reclassified as inverse agonists (Smit et al., 2007), whereas true (neutral) antagonists are difficult to identify for most GPCRs.

Oligomerization occurs in most if not all GPCRs, including several of the histamine receptor subtypes (see sections below). However, it is not clear whether this occurs *in vivo* in all cases and what might be the functional significance of this (Vischer et al., 2011). The majority of the studies have been performed with *in vitro* heterologous systems with recombinant receptors [e.g., H_4 receptor (van Rijn et al., 2006)]. However, there is growing *in vivo* evidence for oligomerization for some classes of GPCRs, including class C GPCRs, for example, $GABA_B$ and metabotropic glutamate receptors. Structures comprising monomers, dimers, and higher-order oligomers of GPCRs have been shown to assemble into transient and/or stable homo-oligomeric and hetero-oligomeric macromolecular complexes. It is unclear whether the individual protomers within a homodimeric structure are always equivalent or play distinct roles in agonist occupancy and/or G protein activation, as appears to be the case in class C GPCRs. The current status of the field was recently nicely reviewed (Ferre et al., 2014). The increased molecular understanding of the histamine receptor proteins has been paralleled by developments in the field of histamine receptor pharmacology. The first histamine receptor antagonist drugs were developed in the 1930s and 1950s, over 20 years after their discovery in 1910 (Simons and Simons, 2011). The H_2 receptor was discovered in the early 1970s (Powell and Brody, 1976) and the H_3 receptor in the early 1980s (Arrang et al., 1983), and finally, the last member to join the group, the H_4 receptor, was identified using molecular biologic techniques at the beginning of the millennium (Nakamura et al., 2000; Liu et al., 2001a; Morse et al., 2001; Nguyen et al., 2001; Zhu et al., 2001; O'Reilly et al., 2002).

The first two receptors have been exploited extremely successfully in the development of a range of “blockbuster” drugs. There is now growing anticipation that the two most recently discovered histamine receptor subtypes will yield further therapeutic success, because ligands for both recently entered clinical development, with the H_3 receptor antagonist, pitolisant (Wakix) being filed for licensing by Bioprojet (Paris, France) in May 2014. The field waits to see if this filing is successful. In a similar fashion, although some positive results have been reported for H_4 receptor ligands in early clinical trials, the first H_4 receptor drug is yet to be filed and registered.

Gene-targeted histidine decarboxylase (HDC) knockout (KO) mice have provided a large amount of information regarding the role of histamine. These mice are viable, fertile, and display no gross abnormalities except for abnormal mast cells (Ohtsu et al., 2001). However, there are permanent changes in the cortical-electroencephalogram and sleep-wake cycle: At moments when high vigilance is required, mice lacking brain histamine are unable to remain awake, a

prerequisite condition for responding to behavioral and cognitive challenges (Parmentier et al., 2002), changes in learning ability (Dere et al., 2003), and increased obesity in high-fat diet-fed mice (Haas et al., 2008).

The combinatorial roles of all four histamine receptors were studied in autoinflammatory disease of the nervous system in the search of an effective therapy for multiple sclerosis. H₁ receptor, H₂ receptor-KO mice developed less severe experimental autoimmune encephalitis (EAE) than H₃ receptor-, H₄ receptor-KO mice (Saligrama et al., 2012). Teuscher's group (Saligrama et al., 2013) also compared the phenotypes of H_{1,2,3,4} receptor- and HDC-knockout mice; unexpectedly and interestingly they displayed opposite phenotypes.

This review will focus on the advances in our understanding of histamine pharmacology that have occurred since the last review published in 1997 (Hill et al., 1997). Histamine receptors can be accessed through the International Union of Basic and Clinical Pharmacology/British Pharmacological Society Guide to Pharmacology (Alexander et al., 2013; <http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=33>).

II. Histamine H₁ Receptor

The first histamine receptor has been known since its pharmacological characterization using antagonists (Bovet and Staub, 1937) and agonists (Black et al., 1972). It was identified as a glycoprotein (Garbarg et al., 1985) and cloned in 1991 (Yamashita et al., 1991). It is very widely expressed throughout the body in epithelial, vascular, smooth vascular, neuronal, glial, and immune cells (Hill et al., 1997; Haas et al., 2008; Shimamura et al., 2011). This receptor is responsible for the early biologic method to determine histamine by contraction of guinea pig ileum preparations and most of the symptoms caused by histamine in allergy and asthma, except the inflammatory component.

A. Receptor Structure

As all four histamine receptors, the H₁ receptor belongs to the GPCR family. The bovine H₁ receptor cDNA was cloned in 1991 by expression cloning in the classic *Xenopus* oocyte system (Yamashita et al., 1991). This led rapidly to the cloning of the receptor cDNA in several species, including human in 1993 and 1994 (De Backer et al., 1993; Moguilevsky et al., 1994). The human gene was subsequently localized to chromosome 3p14-p21 (Le Coniat et al., 1994). A single H₁ receptor polymorphism rs7651620 Glu270Gly has been identified that is relevant to African subjects only (Garcia-Martin et al., 2009; Micalef et al., 2013).

On the basis of immunoprecipitation, time-resolved fluorescence resonance transfer and mutagenesis approaches, there is strong evidence that the H₁ receptor

is expressed as both homomeric and oligomeric structures. Furthermore, evidence has been provided for the presence of robust domain-swapped H₁ receptor dimers in which there is a reciprocal exchange of TM6 and 7 between the individual monomers in the dimer (Bakker, 2004).

Structural biology in GPCRs recently received tremendous input with the solved crystal structures of numerous GPCR family members, including many biogenic amine receptors (for a complete list, see, e.g., <http://www.gpcr.org/7tm/> or <http://zhanglab.ccmb.med.umich.edu/GPCRSDB/>). In 2011, the 3.1 Å resolution structure of a stabilized mutant human H₁ receptor in complex with the first generation H₁ receptor antagonist doxepin was reported (Shimamura et al., 2011). Crystallization was made possible by a replacement of the large third intracellular loop with T4-lysozyme fusion protein (H₁ receptor-T4L) and numerous other technical advances. Doxepin stabilizes the H₁ receptor in an inactive (R) state by preventing movements in the so-called "toggle switch" in TM6, an element proposed to be important in activation in many GPCRs. Obviously, on the basis of phylogenetic relationships, the H₁ receptor shares more structural similarities with the other aminergic receptors than with the more distant GPCRs. Some common motifs in the TM region can be recognized [TM3: D(E)RY; TM6: CWxP; TM7: NPxxY], as well as a disulfide bond that connects the long extracellular loop 2 (ECL2) with the extracellular end of TM3 (Shimamura et al., 2011). Interestingly, the palmitoylation site at the end of TM7, which has often been recognized as a membrane anchor, is missing in H₁ receptor (Fig. 2).

The binding pocket of doxepin involves the highly conserved Asp107^{3,32} in TM3 and aromatic residues in TMs 5 and 6 (e.g., Phe424^{6,44}, Trp428^{6,48}, and Phe432^{6,52} (Shimamura et al., 2011), as previously had been assumed for related H₁ receptor antagonists based on site-directed mutagenesis and homology modeling exercises (Ohta et al., 1994; Nonaka et al., 1998; Wieland et al., 1999). The strong hydrophobic interactions of the aromatic moieties of doxepin with Trp428^{6,48} may prevent movement of helix 6, which is generally seen as one of the hallmarks of GPCR activation. Doxepin binds relatively deep in the binding pocket defined by TM3, -5, and -6. Interestingly, in the X-ray structure an additional phosphate-anion binding site at the entrance of the ligand-binding pocket is observed as a novel feature. The phosphate anion is coordinated by Lys179^{ECL2}, Lys191^{5,39}, and His450^{7,35}, and this binding pocket is suggested to play a role in the interaction with the second generation zwitterionic antihistamines (Shimamura et al., 2011). Evidence for a role of Lys191^{5,39} and extracellular domains of the H₁ receptor in ligand-receptor interactions has earlier been obtained by mutagenesis and molecular dynamics studies (Wieland et al., 1999;

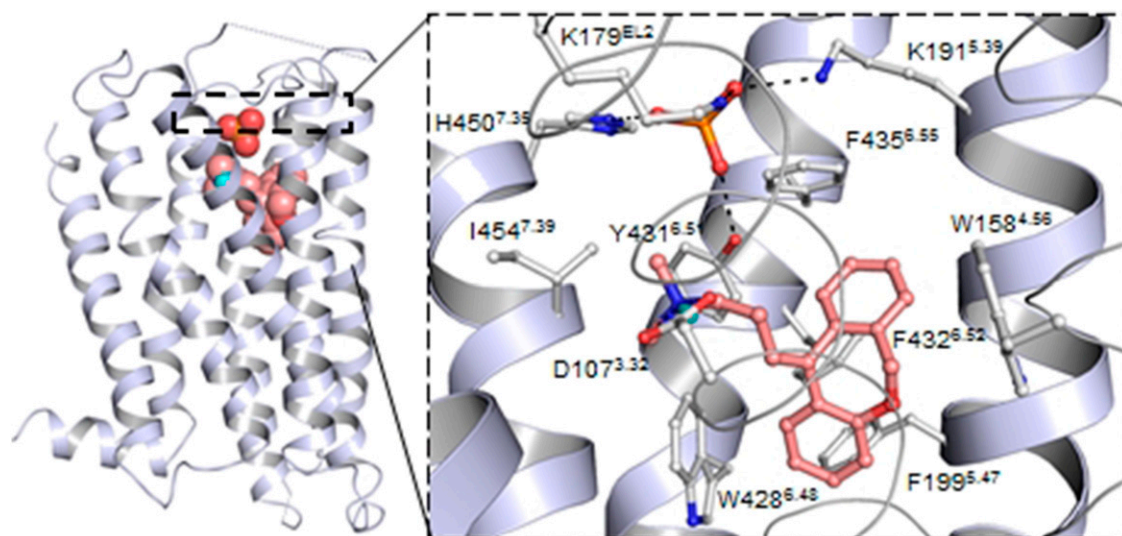


Fig. 2. Overall 7TM X-ray structure of the H₁ receptor (PDB ID 3RZE) bound with the tricyclic H₁ receptor inverse agonist doxepin and a phosphate ion and a close-up on the binding site with residues surrounding doxepin and the phosphate ion. Residues are numbered as found in the human H₁ receptor sequence and with the corresponding Ballesteros-Weinstein numbering.

Gillard et al., 2002a; Strasser and Wittmann, 2007; Wittmann et al., 2011b). Insights into the molecular features governing agonist-induced H₁ receptor activation await the resolution of an active H₁ receptor X-ray structure and currently still rely on molecular modeling and/or mutagenesis studies (Ohta et al., 1994; Jongejan et al., 2005; Strasser et al., 2008b; Sansuk et al., 2011). Histamine is thought to bind the H₁ receptor with its protonated ethylamine side chain via Asp107^{3.32} (Ohta et al., 1994), whereas the imidazole ring is thought to interact with Asn198^{5.46} and Lys191^{5.39} (Leurs et al., 1994a, 1995a). The interaction of the protonated side chain with Asp107^{3.32} allows potentially for the release of Ser^{3.36}, allowing it to act as a toggle switch and to interact with Asn^{7.45} in the active state of the receptor (Jongejan et al., 2005) (Fig. 3; Table 1).

B. Signal Mechanisms

The human H₁ receptor produces its action mainly by coupling to G_{q/11} proteins (Gutowski et al., 1991; Leopoldt et al., 1997; Selbach et al., 1997; Moniri et al., 2004), but also signals via G_{i/o} in some systems (Seifert et al., 1994; Wang and Kotlikoff, 2000), and the small G protein family, most likely through an indirect downstream effect (Mitchell and Mayeuddin, 1998). Direct interaction of the H₁ receptor with G_{q/11} was recently visualized in real time in HELA cells endogenously expressing H₁ receptor (Adjobo-Hermans et al., 2011).

The major signaling pathway for H₁ receptor elicits activation of phospholipase C, which produces 1,2-diacylglycerol and inositol-1,4,5-trisphosphate, leading to activation of protein kinase C (PKC), catalyzing the Ser/Thr phosphorylation of multiple downstream mediators and release of calcium ions from intracellular

stores, respectively (Hill et al., 1997). This leads to calcium ion entry through calcium channels, cation channels of the transient receptor potential channel type (Brown et al., 2002; Doreulee et al., 2003), and stimulation of a Na⁺/Ca²⁺ exchanger (Eriksson et al., 2001; Sergeeva et al., 2003). Nicotinic acid adenine dinucleotide phosphate (NAADP) has also been suggested as a potential second messenger in histamine-induced Ca²⁺ release from lysosome-like acidic compartments, functionally coupled to the endoplasmic reticulum via H₁ receptor in endothelial cells. By using the human EA.hy926 endothelial cell line and primary human umbilical vein endothelial cells, selective H₁ receptor activation increases intracellular NAADP levels, and Ca²⁺ release was shown to involve both acidic organelles and the endoplasmic reticulum. Furthermore, H₁ receptor-induced von Willebrand factor secretion has been shown to require a specific Ca²⁺ signaling and NAADP mechanism (Esposito et al., 2011) (Fig. 4).

H₁ receptors also mediate the production of arachidonic acid, nitric oxide, and cyclic GMP (Richelson, 1978; Snider et al., 1984; Leurs et al., 1994b; Prast and Philippu, 2001) through G_i/G_o protein-mediated activation of phospholipase A₂, [Ca²⁺]_i-dependent nitric oxide (NO) synthases, and NO-dependent guanyl cyclases, respectively. NO is thought to be involved in the histamine-induced suppression of AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor-mediated synaptic currents in supraoptic neurons through activation of H₁ receptor. Histamine is believed to act initially at supraoptic cells (perhaps both neuronal and non-neuronal) to induce the production of NO, which then locally modulates synaptic transmission via a post-synaptic mechanism (Li and Hatton, 2000). Stimulation of the H₁ receptor also increases endothelial NO synthase transcription in human vascular endothelial

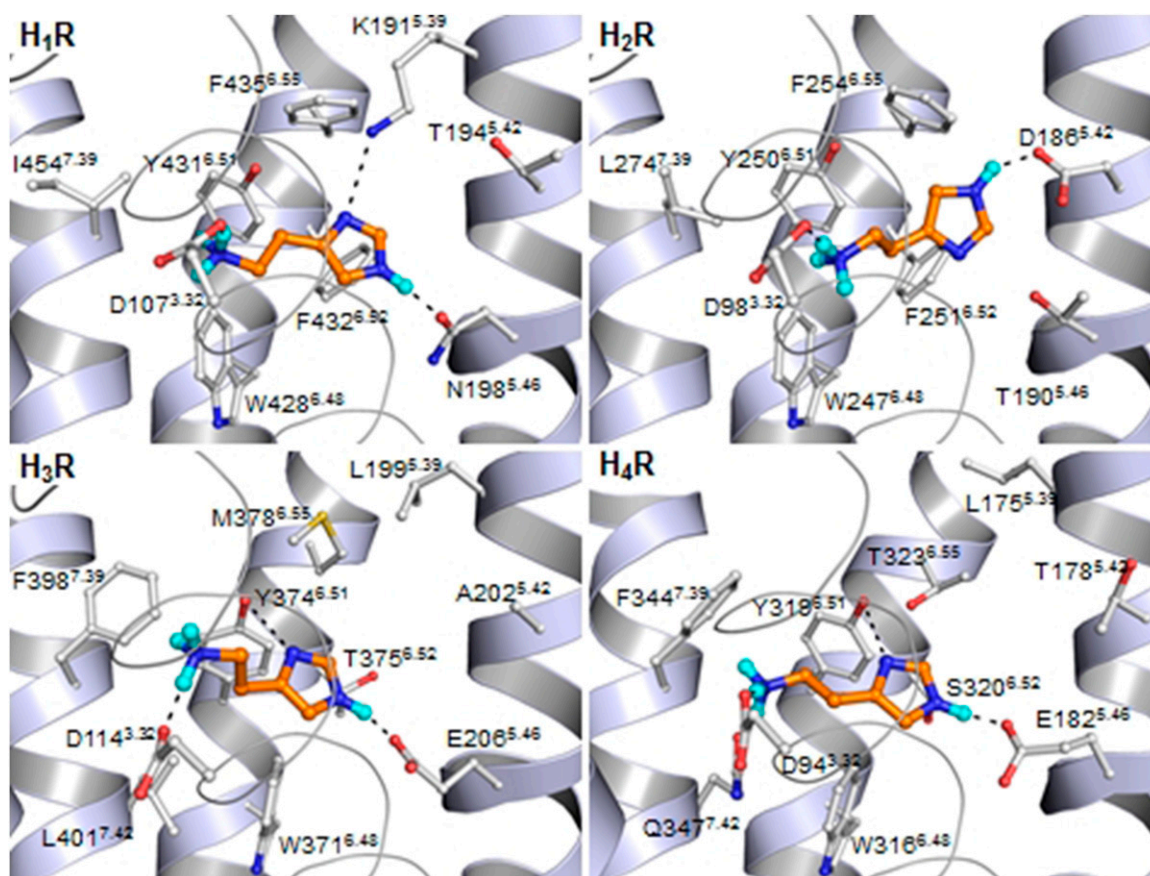


Fig. 3. Binding of histamine in the four different histamine receptors as based on mutagenesis data and docking studies in the H₁ receptor X-ray structure and H₂ receptor–H₄ receptor homology models, based on the H₁ receptor X-ray structure. Residues are numbered as found in the human sequences and with the corresponding Ballesteros-Weinstein numbering.

cells via a Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) signaling pathway, which may be protective under normal conditions, but in contrast, may be deleterious under conditions of oxidative stress, when endothelial NO synthase can produce reactive oxygen species at the expense of NO (Li et al., 2003). Histamine,

through H₁ receptors, increases endothelial NO production as an endothelium-dependent vasodilator but acts as a vasoconstrictor in atherosclerotic coronary arteries.

In the mammalian brain, adrenal glands, and CHO cells, activation of the H₁ receptor also stimulates

TABLE 1
Overview human histamine receptor subtypes (*hH₁* receptor-*hH₄* receptor).

	<i>hH₁</i> R	<i>hH₂</i> R	<i>hH₃</i> R	<i>hH₄</i> R
Chromosomal gene location	3q25	5q35.2	20q13.33	18q11.2
Amino acids	487	359	445	390
Isoforms			at least 20 (65, 66)	>3
G protein coupling	G $\alpha_{q/11}$	G α_s	G $\alpha_{i/o}$	G $\alpha_{i/o}$
Constitutive activity	+	+	++	++
Signal transduction	PLC \uparrow , Ca ²⁺ \uparrow	cAMP \uparrow	cAMP \downarrow , Ca ²⁺ \uparrow , MAPK \uparrow	cAMP \downarrow , Ca ²⁺ \uparrow , MAPK \uparrow
Tissue localizations	Ubiquitous (mainly lung, CNS, blood vessels)	Ubiquitous (mainly stomach, heart, CNS)	Neurons (CNS and PNS)	Bone marrow, hematopoietic cells
Physiologic relevance	Bronchoconstriction, vasodilation, food intake, sleep-wake regulation	Gastric acid secretion	Neurotransmitter release (\rightarrow sleep-wake regulation, attention/cognition, food intake)	Immune responses (\rightarrow chemotaxis, IL-, IFN-modulation)
Pathophysiological conditions	Allergic reactions, emesis, sleep-wake disorders	Gastric ulcers	Cognitive impairment, schizophrenia, sleep-wake disorders, epilepsy, pain, etc.	Inflammatory diseases (allergy, asthma, pruritus, arthritis), pain, etc.

+ and ++, extent of constitutive activity; PL, phospholipase; PNS, peripheral nervous system.

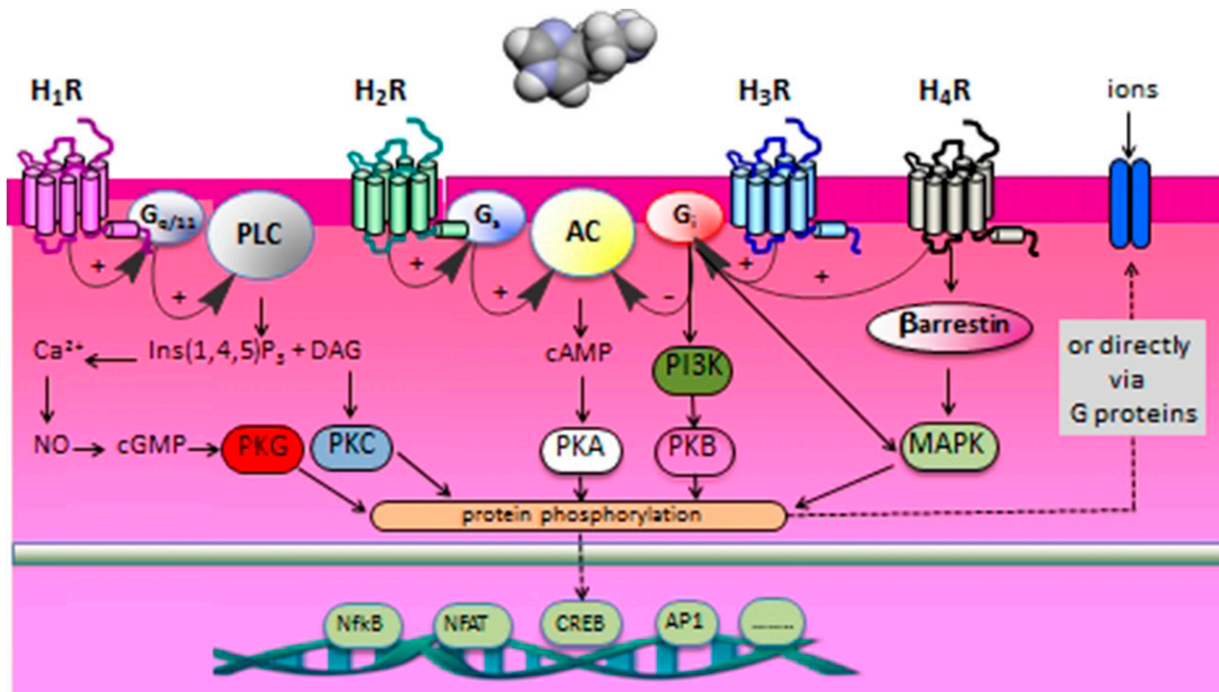


Fig. 4. Schematic overview of the main signal transduction routes of the four different histamine receptors.

adenylyl cyclase and consequently cAMP production, the canonical signaling pathway of the H₂ receptor (see below). In rat brain, the cAMP production is dependent upon PKC activation and intra- and extracellular calcium ion levels (Marley et al., 1991). In the adrenal gland, H₁ receptor activation of adenylyl cyclase is dependent on extracellular Ca²⁺ only (Marley et al., 1991). The stimulatory effects of histamine on cAMP production are most likely not mediated directly through G_s coupling but rather indirectly via an increase in [Ca²⁺]_i and the release of activated Gβγ-subunits. For example, the neuronally expressed adenylyl cyclase 1 is a paradigm for a Ca²⁺/calmodulin-stimulated adenylyl cyclase (Sunahara and Taussig, 2002).

H₁ receptor activation in transfected CHO cells increases forskolin-dependent cAMP production, which is independent of extracellular Ca²⁺ and PKC activation and is pertussis toxin-insensitive (Leurs et al., 1994b). Stimulation of H₁ receptors activates adenylyl cyclase in CHO cells relies on the release of Gβγ-subunits from G proteins, thereby elevating intracellular cAMP concentrations (Maruko et al., 2005).

It is well established that histamine modulates cell proliferation through the activation of the H₁ receptor. The H₁ receptor can signal to the nucleus via PKCα subsequent to activation of phospholipase Cβ (Megson et al., 2001). Functional coupling of the H₁ receptor to G_q-phospholipase C (PLC) leads to the activation of RhoA and Rac small GTPases through a direct interaction of activated G_α-subunits with p63RhoGEF and suggest distinct roles for Rho GTPases in the control of cell proliferation by histamine that has

relevance in cancer biology (Valencia et al., 2001; Lutz et al., 2007; Notcovich et al., 2010). Moreover, also the canonical β-catenin pathway is activated downstream of the H₁ receptor in a variety of cell types. Stimulation of the H₁ receptor elicits transactivation of a T-cell factor/β-catenin-responsive construct in HeLa cells and in the SW-480 colon cell line. Furthermore, histamine treatment increases phosphorylation of glycogen synthase kinase 3-β in HeLa cells, murine macrophages, and DLD-1, HT-29, and SW-480 colon cell lines, whereas histamine also decreases the phosphorylated β-catenin content in HeLa cells and murine macrophages (Diks et al., 2003).

The H₁ receptor displays constitutive receptor activation in the absence of agonists (Bakker et al., 2000; Jacoby et al., 2006), as measured by, e.g., inositol phosphate production and nuclear factor-κB reporter gene activation. This finding resulted in the reclassification of H₁ receptor ligands; agonists activate the receptor (2–5), inverse agonists inhibit the constitutive activity and neutral antagonists inhibit the actions of both agonists and inverse agonists without modifying constitutive activity. All the “classical” antihistamines are indeed inverse agonists (Bakker et al., 2000) (6–16), while the experimental ligands, histabudifen and histapendifen are neutral antagonists (Govoni et al., 2003). These latter compounds may allow the study of in vivo relevance of H₁ receptor constitutive antagonism, which remains to be elucidated. As with many GPCRs, the extent of H₁ receptor constitutive activity depends on the specific parameter determined (Bakker et al., 2007; Appl et al., 2012). The high

constitutive activity of the H₁ receptor upon assessment of distal signaling parameters, i.e., reporter gene expression, may be explained by the fact that the concentration of effectors is limiting the cascade so that even a small number of constitutively active H₁ receptor results in a high agonist-dependent signal. In fact, in native systems, there is little evidence to date for high constitutive H₁ receptor activity.

A growing number of studies have also provided evidence for the concept of multiple signaling pathways activated by a single receptor (functional selectivity, biased signaling or ligand-specific receptor conformations) (Moniri and Booth, 2004; Galandrin et al., 2007; Kobilka and Deupi, 2007; Kenakin, 2011; Seifert et al., 2011). One of the first studies to support the concept of agonist-dependent functional selectivity at the H₁ receptor used the two H₁ receptor ligands, (\pm)-*cis*-5-phenyl-7-dimethylamino-5,6,7,8-tetrahydro-9H-benzocycloheptane (*cis*-PAB) and ($-$)-*trans*-1-phenyl-3-dimethylamino-1,2,3,4-tetrahydronaphthalene (*trans*-PAT) derived from the same chemical class (but with distinct stereochemistry) which were shown to display functional selectivity, the former stimulating cAMP production and the latter, PLC/inositol-1,4,5-trisphosphate metabolism (Moniri et al., 2004). However, as for constitutive H₁ receptor signaling, currently there is no evidence for the importance of biased signaling *in vivo*.

The H₁ receptor-mediated signaling cascade is known to desensitize quickly (Smit et al., 1992; McCreath et al., 1994) via both PKC-dependent and -independent mechanisms. GPCR kinase 2 is the principal GPCR kinase mediating agonist-induced H₁ receptor desensitization in HEK293 cells (Iwata et al., 2005). The H₁ receptor-mediated signaling, furthermore, can be inhibited by phorbol ester-induced PKC activation. Two amino acid residues (Ser396, Ser398) have been

shown to be PKC phosphorylation sites by *in vitro* phosphorylation studies using a series of synthetic peptides. Moreover, treatment with phorbol ester decreased histamine-induced accumulation of inositol phosphates in CHO cells expressing the H₁ receptor. Site-directed mutagenesis studies showed that Ser398 was the principle residue involved in PKC-mediated desensitization (Fujimoto et al., 1999) (Fig. 5).

C. Anatomic Framework

H₁ receptors are found throughout the whole body and nervous system with considerable variations among species (Chang et al., 1979). H₁ receptors are expressed in vascular and airway smooth muscle, chondrocytes, hepatocytes, endothelial cells, dendritic cells, monocytes, neutrophils, T and B cells (Jutel et al., 2001, 2009; Toghiani, 2003). The distribution in the brain is uneven, and because of the circuit organization of the central nervous system (CNS), the anatomy is particularly relevant. Some of the early studies on localization and physiologic/pharmacological implications of H₁ receptors, discussed extensively in Hill et al. (1997), are only listed here: blood vessels (Barger and Dale, 1910; Dale and Laidlaw, 1910; Folkow et al., 1948; Black et al., 1972), other smooth muscle preparations (Marshall and Cherry, 1955; Ash and Schild, 1966; Black et al., 1972; Hill, 1990) and heart (Sakuma et al., 1988). The distribution of H₁ receptors in different mammalian tissues was first studied using selective radioligands such as [³H]mepyramine (Hill et al., 1977), later using *in situ* hybridization (Fig. 5). [¹¹C]Mepyramine (cf. 8) and [¹¹C]doxepin have also proved useful for imaging H₁ receptors in the living human brain (Villemagne et al., 1991; Yanai et al., 1992).

H₁ receptor stimulation leads to endothelial cell contraction and thus increases vascular permeability,

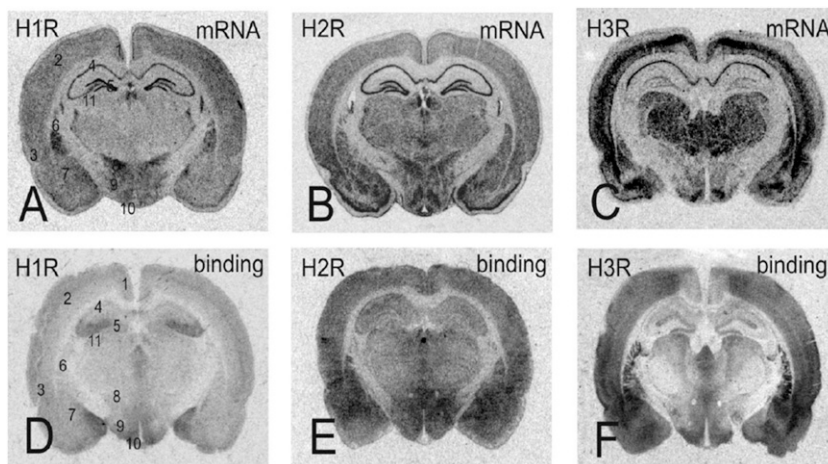


Fig. 5. Expression and receptor radioligand binding to cross sections of the rat brain. Data are shown for both mRNA distribution from *in situ* hybridization films and autoradiograms after labeling with radioactive ligands for each receptor. For identification of the brain areas, the following areas are marked in (A–D): 1, retrosplenial granular cortex; 2, primary somatosensory cortex; 3, entorhinal cortex; 4, CA1 area of the hippocampus; 5, dentate gyrus; 6, caudate putamen; 7, amygdala; 8, zona incerta; 9, lateral hypothalamic area; 10, arcuate nucleus; 11, dorsal lateral geniculate nucleus. Modified from Haas and Panula (2003).

and the release of several bioactive substances including nitric oxide. H₁ receptors also modulate the action of chromaffin cells in the adrenal medulla and lymphocytes (see Hill et al., 1997). An autoimmune disease locus, *Bphs* has been identified as H₁ receptor (Ma et al., 2002). Endothelial H₁ receptor signaling reduces blood-brain barrier permeability and susceptibility to autoimmune encephalomyelitis (Saligramam et al., 2012).

H₁ receptors are widely distributed in mammalian brain (Hill, 1990; Schwartz et al., 1991). Particularly high densities are found in brain regions concerned with neuroendocrine, behavioral, and nutritional state control, including the periventricular, suprachiasmatic, and ventromedial nuclei of the hypothalamus, aminergic and cholinergic brainstem nuclei, thalamus, and cortex (Schwartz et al., 1991). In human brain, the highest [³H]mepyramine binding is found in the cerebral cortex and the infralimbic structures (Martinez-Mir et al., 1990), in keeping with the mapping of the H₁ receptor using [¹²⁵I]iodobolpyramine autoradiography in the guinea pig (Bouthenet et al., 1988). The distributions in rat (Palacios et al., 1981a) and guinea pig (Palacios et al., 1981b) are similar to each other and to humans with some exceptions: the guinea pig cerebellum shows high density (Chang et al., 1979; Hill and Young, 1980; Bouthenet et al., 1988; Ruat and Schwartz, 1989) in contrast to the low density in the rat, and the rat thalamus shows a clearly lower H₁ receptor mRNA expression than the guinea pig (Lintunen et al., 1998). In most brain areas, there is overlap of H₁ receptor binding sites and messenger ribonucleic acid levels except in hippocampus, where the pyramidal cell layer shows high mRNA expression and molecular layer high radioligand binding (Lintunen et al., 1998), and cerebellum in which the discrepancy is likely to reflect the presence of abundant H₁ receptors in dendrites of pyramidal and Purkinje cells, respectively (Traiffort et al., 1994). In the hippocampus, both the H₁ receptor mRNA expression and radioligand binding sites are in clear contrast with the low density of histamine-containing nerve fibers (Lintunen et al., 1998), which suggests that the turnover of histamine in hippocampus is rapid. Figure 5 shows the distribution of H₁ receptor mRNA in the rat brain at midhypothalamic level in comparison with corresponding H₁ receptor radioligand binding profiles. These patterns are also shown in comparison for H₂ receptors and H₃ receptors. Kainic acid-induced limbic seizures rapidly upregulate H₁ receptor mRNA expression in the rat caudate, putamen, and granular layer of the dentate gyrus (Lintunen et al., 1998). This effect is in line with the findings on the protective role of histamine through H₁ receptor versus kainic acid induced hippocampal damage (Kukko-Lukjanov et al., 2006). In immature mice, H₁ receptor activation also plays a pivotal role in regulation of seizure intensity and duration, and seizure-induced neuronal damage (Kukko-Lukjanov et al., 2010).

In human brain, higher densities of H₁ receptor radioligand binding sites are found in neocortex, hippocampus, nucleus accumbens, thalamus, and posterior hypothalamus, whereas cerebellum and basal ganglia show lower densities (Chang et al., 1979; Kanba and Richelson, 1984; Martinez-Mir et al., 1990; Villemagne et al., 1991; Yanai et al., 1992). In human prefrontal cortex, the highest mRNA expression is found in deep layers IV, V and VI, with slightly higher levels in layer V than the other layers in most areas (Jin and Panula, 2005). The [³H]mepyramine binding levels is highest in layer III of the prefrontal cortex, suggesting that the apical dendrites of neurons in the deep laminae contain H₁ receptors (Jin and Panula, 2005). In human thalamus, the anterior, medial, central and lateral nuclear region in dorsal and medial parts of the thalamus show higher H₁ receptor mRNA expression than posterior and ventral parts (Jin et al., 2002). Although [³H]mepyramine is also detectable throughout thalamic nuclei, it is modest and many of the H₁ receptor expressing neurons are likely to project to the cerebral cortex (Jin et al., 2002). With availability of appropriate positron emission tomography (PET) tracers ([¹¹C]pyrilamine and [¹¹C]doxepin) in the early 90s (Yanai et al., 1992), H₁ receptor distribution and occupancy in humans have also been mapped using functional imaging techniques (Yanai and Tashiro, 2007) to study the sedative properties and blood-brain barrier permeability of H₁ receptor antagonists (Tashiro and Yanai, 2007), aging (Yanai et al., 1992), and neuropsychiatric disorders, such as Alzheimer's disease, schizophrenia (Iwabuchi et al., 2005), and depression (Kano et al., 2004), in all of which H₁ receptor binding was found to be lower than in age-matched healthy controls (Fig. 6).

D. Function

Calcium ion influx leads to depolarization and contraction of smooth muscle cells. This is a classic experimental pharmacological setting used in teaching and research. For example, in guinea pig ileum smooth muscle preparations, H₁ receptor antagonists concentration-dependently inhibit histamine-induced contraction, which offers a simple and quantitative ex vivo testing system for H₁ receptor ligands. Guinea pig trachea and rat aortic rings offer further smooth muscle preparations frequently used in pharmacological assay systems. Following the cloning of the H₁ receptor, it became possible to express the receptor in heterologous systems and measure [Ca²⁺] levels or inositol phosphate hydrolysis directly in vitro. This has enabled further advances in understanding of H₁ receptor signaling. Using transfected cells, it was shown that via both Gα_{q/11}- and Gβγ-subunits human H₁ receptors can activate nuclear factor-κB, a transcription factor prominent in inflammation (Bakker et al., 2001).

H₁ receptor activation excites neurons in most brain regions, including brain stem (Lin et al., 1996; Barbara et al., 2002; Korotkova et al., 2005), hypothalamus

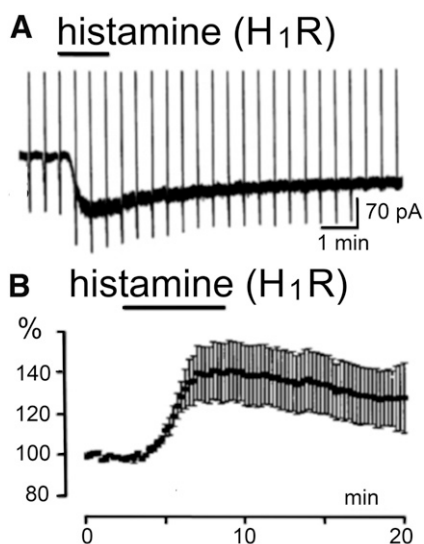


Fig. 6. Excitation of rat brainstem neurons by histamine through H₁ receptor activation. (A) Inward current in a dorsal raphe neuron with increase in channel noise indicating (transient receptor potential channel-type) channel openings. (B) Increase in firing rate of 15 GABAergic (averaged) neurons in the substantia nigra (modified from Brown et al., 2002, and Korotkova et al., 2002).

(Tabarean, 2013), thalamus (McCormick and Williamson, 1991; Soria-Jasso et al., 1997; Zhou et al., 2006), amygdala, septum (Gorelova and Reiner, 1996; Xu et al., 2004), hippocampus (Selbach et al., 1997; Manahan-Vaughan et al., 1998), olfactory bulb (Jahn et al., 1995), and cortex (Reiner and Kamondi, 1994) through an increase of $[Ca^{2+}]_i$. Figure 6 illustrates examples of inward current and increased firing frequency. This can, however, also evoke hyperpolarization and inhibition by the opening of Ca^{2+} -dependent K^+ channels, for instance in the hippocampus. H₁ receptor activation can thus evoke bidirectional and synergistic effects (Garbarg and Schwartz, 1988; Ruat et al., 1992; Bakker et al., 2004a; Dai et al., 2006), for example, reduction or amplification of H₂ receptor actions depending on the timing and context of receptor activation (Baudry et al., 1975; Garbarg and Schwartz, 1988; McCormick and Williamson, 1989; Selbach et al., 1997).

Removal of the H₁ receptor in KO mice (Hirai et al., 2004; Huang et al., 2006; Masaki and Yoshimatsu, 2006) produces immunologic (Jutel et al., 2001), metabolic, and behavioral state abnormalities similar to those observed in HDC-KO mice (Parmentier et al., 2002), indicating that the excitation mediated by H₁ receptors is the major mechanism for the cortical activation during waking. This is also in keeping with the well known sedative action of the H₁ receptor antagonists (Bovet, 1950), which function as inverse agonists, stabilizing the receptor in its inactive state (R) (Lin et al., 1996; Bakker et al., 2002, 2007; Jongejan et al., 2005). Many antidepressant and antipsychotic drugs also bind to the H₁ receptor (Richelson, 1978; Kim et al., 2007). A recent analysis of rare copy

variants in Tourette syndrome families indicated a strong association with histaminergic signaling, particularly within H₁ receptor pathways (Fernandez et al., 2012).

E. H₁-Selective Ligands

Despite the fact that histamine regulates numerous physiologic and pathophysiological effects via H₁ receptors, the research area of the corresponding agonistic active compounds has been neglected for a long time. Modifications of the endogenous ligand led to 2-(thiazol-2-yl)ethanamine (**2**) and later to 2-(3-bromophenyl)histamine or 2-(3-(trifluoromethyl)phenyl)histamine (**3**) (Fig. 7). Although the well characterized 2-(thiazol-2-yl)ethanamine shows only a moderate efficacy of about 26% of that of histamine with a partial agonist behavior, it clearly demonstrated that the tautomeric shift on the imidazole nitrogen atoms is not an essential structural element. Also with other nonimidazole heterocyclic compounds such as the ergot derivative lisuride (partial) agonist properties intrinsic activity from 0.27 to 1.0 (intrinsic activity of histamine = 1.0) could be observed (Bakker et al., 2004b; Pertz et al., 2004). 2-Phenylhistamines were initially developed as H₁ receptor ligands. However, a recent study revealed that the histamine receptor subtype is selectivity strongly affected by N^α -substitution. In contrast to the corresponding primary amines, the N^α -methylated phenylhistamines (KK62) have significantly higher affinity for the H₄ receptor than the H₁ receptor (Strasser et al., 2009; Wittmann et al., 2011a). Compounds with higher maximal efficacies than that of histamine could be obtained by histamine substitution in the 2-position by a diphenylpropyl moiety. This class of histaprodifens is supposed to simultaneously occupy an agonist as well as an antagonist binding site as shown by site-directed mutagenesis studies and molecular modeling techniques (Bruyters et al., 2004), showing slight improvement in efficacy from histaprodifen (**4**) over methylhistaprodifen to supra-histaprodifen (**5**) (Jongejan and Leurs, 2005). The distance of three methylene groups between the diphenyl structure and the imidazole ring seems to be crucial as shorter chains led to partial agonists and longer alkyl bridges to antagonists. Phenoprodifens, combining a phenylhistamine and histaprodifen partial structure represent a new class of H₁ receptor partial agonists/neutral antagonists (Strasser et al., 2008a) (Fig. 7).

The relatively low number of H₁ receptor agonists is in contrast to the high number of different H₁ receptor antagonists. Pharmacologically, they are divided into different generations because of their target profile and their unwanted side effects. Most of these compounds, if not all of them, are now pharmacologically more clearly defined as inverse agonists (Bakker et al., 2007), with the extent of inverse agonism being parameter dependent. The first generation “antihistamines”

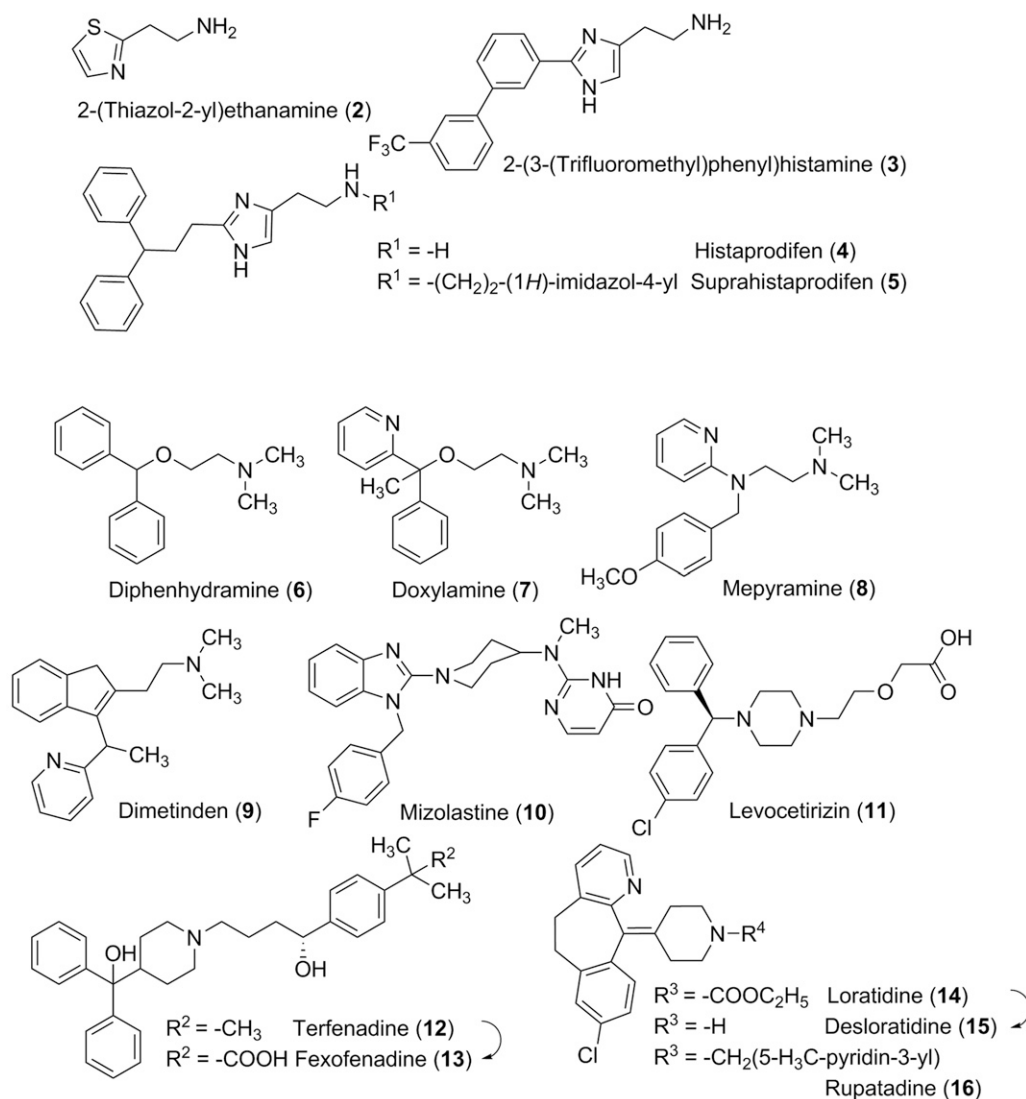


Fig. 7. H_1 receptor ligands.

are structurally described as two aromatic elements linked through a mainly three membered bridge to a basic aliphatic tertiary amino functionality. Diphenhydramine (6), doxylamine (7), mepyramine (pyrilamine; 8), doxepine, dimetinden (9), and bamipine are a few examples based on this general construction pattern. These compounds have in common that they easily cross the blood-brain barrier causing sedation (Nicholson et al., 1991) and/or anticholinergic effects (Hill, 1990). At higher dosages, numerous examples of these compounds also display anesthetic effects that may have some therapeutic advantages on topical applications for urticaria or itch (Orhan et al., 2007; Murota and Katayama, 2011). However, it should also be noted that at high concentrations, first-generation H_1 receptor antagonists, because of their cationic-amphiphilic properties, can also exhibit paradoxical proinflammatory effects that are mediated via a direct and receptor-independent activation of G_T proteins in cells of the immune system (Burde et al., 1996).

The class of (polycyclic) neuroleptics has been developed out of the lead structure of early H_1 receptor antagonists. Therefore, it is not surprising that many of the neuroleptics still possess high H_1 receptor antagonist affinities, causing sedation and weight gain. One may also assume that the antidepressants acting as selective inhibitors of neurotransmitter transporters have been detected by variation of the H_1 receptor antagonist lead structure (e.g., diphenhydramine [6] versus fluoxetine), leading to a different pharmacological profile. It is clear that the members of family A of rhodopsin-like GPCRs share some sequence homology and therefore have comparable recognition areas for some structural motifs. These recurrently revealed fragments are termed privileged structures. The privileged structures can be detected in many compounds targeting the biogenic amine receptors in different combinations for receptor preference. With the H_1 receptor, it is the diaryl element that may be incorporated in a tricyclic

ring system, linked by the short chain to the amino group. By fulfilling all these requirements, the highly potent mepyramine (also called pyrilamine [8]) has often been used as reference antagonist and for radiolabeling studies (Tashiro and Yanai, 2007; Yanai and Tashiro, 2007) (see section II.C).

Ligand binding at the H₁ receptor takes place in a stereoselective manner. The preference of one stereoisomer can be shown by different discriminative ratios for numerous compounds. Depending on the way of stereoselective orientation by stereocenter or stereoaxis and on the receptor interaction, the differences may be up to three orders of magnitude [e.g., *E*-configured (*trans*) triprolidine versus *Z*-configured isomer (*cis*)]. Point mutations in transmembrane helices IV and V show aromatic residues as potential stereoselective discriminators (Trp¹⁶⁷, Phe⁴³³, Phe⁴³⁶) (Wieland et al., 1999). Although with cetirizine the difference between both enantiomers is only 2-fold, the “enantiomeric shift” has been exploited to make the more potent (*R*)-(-) enantiomer (levocetirizine; **11**) (Gillard et al., 2002b; Chen, 2008). With the tricyclic compounds, including cyproheptadine or loratadine (**14**; Fig. 7), some conformational isomers have been observed. Normally these compounds undergo a rapid intraconversion, but in some cases the orientation of the piperidine moiety on the bend ring system remains stable and the remaining atropisomers (conformational enantiomers) can be separated (Remy et al., 1977; Randall et al., 1979). It is unclear if these effects can also be observed in vivo. Most investigations in this direction have been made on guinea pig systems and have been verified for human H₁ receptors mostly for marketed compounds only.

In view of the sedative effects of the first generation antihistamines, their clinical usefulness has proven to be limited (see below), although some of the products are currently available as over-the-counter products as sleep aids. To target the important role of histamine in allergic conditions, the class of second-generation antihistamines has been developed. Second generation H₁ receptor antagonists display substantially reduced central side effects, because they have a lower rate of penetration through the blood-brain barrier due to the presence of polar ionic structures or are high-affinity substrates for ATP-dependent P-glycoprotein or organic anion transport polypeptide efflux pumps (Devillier et al., 2008; Broccatelli et al., 2010). This approach has been realized by taking advantage of the active metabolites of antihistamines (e.g., hydroxyzine and cetirizine [cf. **11**], terfenadine [**12**] and fexofenadine [**13**], ebastine and carebastine, and loratadine [**14**] and desloratadine [**15**] in Fig. 7) or by adding highly polar functional groups into the molecule, e.g., carboxylic acid (levocabastine, olopatidine, efletirizine [zwitterionic compounds] or acylguanidine (mizolastine [**10**]) (Fig. 7). Several of these compounds have successfully replaced the older first-generation H₁ antagonists as

therapeutic agents for allergic disorders (see next section).

In fact, it has been the detrimental interaction of several classic antihistamines with the cardiac hERG1 potassium channels that has triggered the development of these successful drugs. For terfenadine in combination with other CYP3A4 substrates or inhibitors (Bailey et al., 1998) or with liver dysfunction (Kamisako et al., 1995), the plasma levels are highly enhanced, leading to the inhibition of cardiac hERG1 potassium channels that then may lead to lethal arrhythmias as a result of QT prolongation (Salata et al., 1995; Lagrutta et al., 2008). Terfenadine (**12**) and astemizole were eventually withdrawn from the market (Estelle and Simons, 1999) in several, but not all, countries (you can still obtain terfenadine in Germany, for example) when they were associated with the risk of Torsades de Pointes and sudden death due to binding to hERG potassium channels. Although this has been questioned recently (Lu et al., 2012), these unfortunate developments led to fundamental changes in the drug discovery and development process. To predict potential adverse effects due to “antitarget” (“off-target”) binding, hERG screening is now undertaken at an early stage of the discovery process (e.g., Finlayson et al., 2004). After the terfenadine withdrawal it was found that the active zwitterionic metabolite of terfenadine (**12**), fexofenadine (**13**), although it has a slightly lower affinity for H₁ receptors, is devoid of this QT-prolonging side effect and has an improved safety profile (Simpson and Jarvis, 2000). Fexofenadine is also less sedative, because it shows only a limited brain penetration, potentially because of its affinity for P-glycoprotein transporters (Molimard et al., 2004; Obradovic et al., 2007). Most of the second generation antihistamines (e.g., levo-cetirizine and olopatidine) share most of the properties of fexofenadine (**13**), including the zwitterionic nature. These compounds all show clearly improved safety profiles and have had reasonable therapeutic success.

F. Clinical Pharmacology

The prototypical “antihistamine” drugs chlorphenamine, clemastine, cyproheptadine, ketotifen, diphenhydramine (**6**), cyclizine, cinnarizine, buclizine, and promethazine (H₁ receptor antagonists) have a long established place in the treatment of nausea and vomiting and allergy, specifically allergic rhinitis and conjunctivitis and anaphylactic shock, but not asthma (Bartho and Benko, 2013). Antihistamines have been formulated for local application to the nasal mucosa, eye, or skin (and together with mast cell stabilizers such as sodium cromoglicate can delay and diminish the symptoms precipitated by localized or systemic release of histamine) (Kari and Saari, 2012; Ridolo et al., 2014). Oral and topical antihistamines are used in the treatment of hay fever, insect bites/stings, and the combination of antipruritic and sedative effects is

often beneficial in removing symptoms and in restoring sleep in seasonal allergy. The sedative side effects in the workplace, or while driving, are a significant problem with the first-generation of antihistamines and provided the biorational impetus for the development of congeners that were less brain permeant (the H₁ receptor crystal structure explains well the differences between first- and second-generation H₁ receptor antagonists, as discussed previously in section II.A). However, a recent study highlighted the need for caution in using such drugs in older hospitalized patients, with a suggested link to onset of delirium (Rothberg et al., 2013). It is disappointing that we still have no hypnotics that mimic or facilitate/extend physiologic sleep, bearing in mind the pivotal role biogenic amines underpin in sleep physiology, arousal, and circadian regulation (Lin et al., 2011a). Nevertheless, H₁ receptor antagonists have been used rarely as CNS niche drugs. For example, H₁ receptor antagonists have been used for their psychosomatic effects in dermatological conditions (Gupta and Gupta, 1996), cyproheptadine is used in pediatric migraine (Lewis et al., 2004a), and close structural congeners are used as neuroleptics and antidepressants (He et al., 2013; Sato et al., 2013).

Although the newer antihistamines generally display high H₁ receptor affinity and higher selectivity versus nontargets than that of the older ones, side effects can still be observed (notably antimuscarinic effects and sedation when taken with alcohol or other depressant drugs (Simons and Simons, 1999; Yanai et al., 2011). With the patent expiry of many second-generation drugs and their widespread availability over the counter at low costs, the medicine agencies are looking for genuine innovation and novelty: one of the outcomes of this is the development of combination therapies, e.g., anti-inflammatory properties such as inhibition of neuropeptide or leukotriene signaling (Scannell et al., 2004; Beaton and Moree, 2010). One of the most recent compounds to enter this clinically and commercially important market is rupatadine (**16**) (Picado, 2006; Fantin et al., 2008), which blocks both peripheral H₁ receptors and the platelet activation pathway, as a platelet-activating factor antagonist (Merlos et al., 1997). Eflerizine, however, was developed as a topical agent to fit the pharmacophores for H₁ receptor antagonists and inhibitors of lipoxygenase (an enzyme involved in the production of leukotrienes) (Salmun, 2002; Lewis et al., 2004b) but was discontinued in the late phases of development. Regarding the H₁ receptor antagonists already in the pharmacopoeia, few studies have been conducted on teratogenicity or embryotoxicity with high doses of antihistamines in animal testing, and it is recommended that antihistamines should not be used in pregnancy (Gilboa et al., 2014). The lack of any teratogenic effects reported thus far gives some confidence, but there should still be a note of caution

because of the lack of controlled studies in children or pregnancy for the first-generation compounds (Church et al., 2010).

III. Histamine H₂ Receptor

The H₂ receptor was identified pharmacologically in 1972 based on the finding that several physiologic effects of histamine, including the stimulatory effect on gastric acid secretion, increase of heart rate, and inhibition of contraction of rat uterus were not antagonized by mepyramine (Black et al., 1972). Cloning of the H₂ receptor allowed expression studies to be performed, which indicated strong expression in the stomach and brain (Gantz et al., 1991b). Clinically, H₂ receptor antagonists transformed the treatment of dyspepsia, esophageal, and gastric ulcers, a trend that continued until these drugs were largely replaced by proton pump inhibitors. Apart from the brain and stomach, the H₂ receptor is expressed in smooth muscle cells, chondrocytes, endothelial and epithelial cells, neutrophils, eosinophils, monocytes, macrophages, dendritic cells, T and B cells (Jutel et al., 2001, 2009).

A. Receptor Structure

Many years after the development of clinically useful H₂ receptor antagonists, the H₂ receptor was first cloned in 1991 by Gantz and colleagues from a canine genomic library, with subsequent rapid cloning of species orthologs from rat, mouse, guinea pig, and human over the subsequent four years (Gantz et al., 1991b; Ruat et al., 1991; Traiffort et al., 1995; Kobayashi et al., 1996). A single genomic clone was isolated that encoded a 1080-base pair (bp) open reading frame with a deduced 360-amino-acid polypeptide. The multiple transcription initiation sites of the human H₂ receptor gene have been mapped and an 85-bp segment (−610 to −525 bp) immediately upstream of the initiation site was identified to exhibit a strong promoter activity in the gastric adenocarcinoma, MNK45, expressing the H₂ receptor (Murakami et al., 1999). Several H₂ receptor polymorphisms have been observed with changes, located in the gene promoter or in the coding region, including a nucleotide change leading to an Asn217Asp change (Orange et al., 1996a,b; Ito et al., 2000; Garcia-Martin et al., 2009; Micallef et al., 2013). Currently, no consensus has been obtained on a potential link of the Asn217Asp change to schizophrenia (Orange et al., 1996b; Ito et al., 2000).

Currently, there is no direct structural information available for the H₂ receptor. Yet, the H₂ receptor possesses many of the key prototypical amino acid residues common to the family A aminergic GPCRs, and homology modeling on the basis of the published H₁ receptor X-ray structure and available mutagenesis data leads to reasonable models (Fig. 2) for the interaction of histamine with the receptor protein

(Kooistra et al., 2013). Site-directed mutagenesis of residue Asp117^{3.32} in TM3 of the canine H₂ receptor (= Asp98^{3.32} in the human H₂ receptor) led to complete loss of [³H]tiotidine (**31**) binding (Kelley et al., 2001). Mutation of either—alone or simultaneously—did not abolish histamine-induced cAMP but markedly reduced its efficacy. Asp186^{5.42}, although it is essential for [³H]tiotidine antagonism, appears not to be crucial for cimetidine antagonism, indicating both shared and distinct sites (Gantz et al., 1992). On the basis of the mutagenesis data and molecular modeling using an H₂ receptor model based on the H₁ receptor X-ray structure, histamine is thought to bind with a different orientation in the binding pocket (Fig. 3).

B. Signal Transduction Mechanisms

The H₂ receptor stimulates adenylyl cyclase-mediated cAMP formation in membrane preparations from various tissues as well as cAMP accumulation in various native cells (for review, see Hill, 1990, and Hill et al., 1997) and cells expressing recombinant H₂ receptors (Alewijns et al., 1998, 2000; Monczor et al., 2003). As for many adenylyl cyclase-coupled GPCRs, the H₂ receptor stimulates cAMP production via the coupling to G_s proteins, as indicated by, for example, agonist-induced photoaffinity labeling. [α -³²P]GTP azidoanilide showed that agonist-activation of H₂ receptors results in labeling of G_s α -subunits with [α -³²P]GTP azidoanilide in mammalian and insect cell expression systems (Kuhn et al., 1996; Leopoldt et al., 1997). Coupling to G_s proteins is furthermore indicated by studies with GPCR-G α fusion proteins, which has permitted the analysis of H₂ receptor/G_s α coupling with high sensitivity at the level of ternary complex formation (high-affinity complex between agonist-occupied receptor and nucleotide-free G protein), guanine nucleotide exchange, i.e., [³⁵S]GTP γ S binding and steady-state GTP hydrolysis, as well as adenylyl cyclase activation (Kelley et al., 2001; Wenzel-Seifert et al., 2001). H₂ receptor-G_s α fusion proteins were also used to analyze ternary complex formation with guanidine-type agonists, which led to the suggestion that each agonist stabilizes a unique conformation in the H₂ receptor (Kelley et al., 2001; Xie et al., 2006).

The H₂ receptor does not only couple to G_s proteins but also to G_{q/11} proteins, resulting in inositol phosphate formation and increases in cytosolic Ca²⁺ concentration in some, but not all, H₂ receptor expressing cells (for previous reviews, see Hill, 1990, and Hill et al., 1997). Moreover, photoaffinity labeling studies with [γ -³²P]GTP azidoanilide revealed that H₂ receptor can activate both mammalian and insect cell G_q proteins in addition to G_s proteins (Kuhn et al., 1996; Leopoldt et al., 1997), whereas heterologous expression of H₂ receptors in rat cardiomyocytes has also been reported to result in the interaction of recombinantly expressed H₂ receptors with G_{q/11}, next to G_s proteins (Wellner-Kienitz et al., 2003).

Interestingly, in this cell system also the G_s-cAMP-PKO pathway promotes increases in cytosolic Ca²⁺ concentration via the phosphorylation of L-type Ca²⁺ channels (Wellner-Kienitz et al., 2003).

The H₂ receptor was the first histamine receptor subtype for which constitutive activation of adenylyl cyclase has been firmly established for both rat (Smit et al., 1996a) and human variants (Alewijns et al., 1998, 2000; Monczor et al., 2003). Clinically used H₂ receptor antagonists, including cimetidine (**24**) and ranitidine (**25**), behaved as inverse agonists, whereas up to now only burimamide has been described as neutral antagonist (Smit et al., 1996a). Interestingly, both rat and human H₂ receptors are upregulated by prolonged receptor occupancy with inverse agonists (Smit et al., 1996a), most likely via both a reduction of cAMP-protein kinase A-mediated downregulation and a stabilization of an inherent structural instability of the H₂ receptor (Alewijns et al., 1998, 2000). So far the physiologic relevance and the structural basis of the constitutive activity of H₂ receptors remain to be determined, but it is interesting to note that prolonged exposure of rabbit parietal cells to H₂ receptor antagonists leads to an upregulation of H₂ receptor protein, adenylyl cyclase, and ultimately to hypersecretion (Takeuchi et al., 1999). Moreover, the reported G649 allelic variant (Asn217Asn) of the human H₂ receptor is reported to have reduced constitutive activity, lower histamine responses, and a diminished upregulation by ranitidine (Fukushima et al., 2001).

With respect to biased signaling, only limited information is currently available for the H₂ receptor. A recent study reported that the inverse agonists ranitidine and tiotidine display positive efficacy toward extracellular signal-regulated kinase (ERK) 1/2 via a mechanism that involves G $\beta\gamma$ -subunits in both transfected HEK-293T cells and human gastric adenocarcinoma cells (Alonso et al., 2014). These findings suggest that H₂ receptor biased signaling might be an important concept to consider.

As with many other GPCRs, the H₂ receptor is desensitized and internalized upon agonist stimulation (Smit et al., 1996b; Fukushima et al., 1997). Truncations or replacements within the C-terminal tail of the receptor revealed that Thr315 was a crucial residue in agonist-dependent internalization but not desensitization (Smit et al., 1996b). Desensitization of the H₂ receptor is suggested to involve both GPCR kinase 2 and 3 (Rodriguez-Pena et al., 2000; Fernandez et al., 2011). The C-terminal tail is required for membrane targeting through a putative palmitoylation-mediated mechanism (Fukushima et al., 1997), and the last 51 amino acids are reported to be crucial for internalization (Fernandez et al., 2008). Recently, the GTPase dynamin has been identified as a binding partner for the H₂ receptor, both in vitro and in vivo (Xu et al., 2008). A role of dynamin, β -arrestin, and clathrin in H₂ receptor

internalization has indeed also been reported (Fernandez et al., 2008).

C. Anatomic Framework

In addition to stomach and brain, in which the expression level is high, the H₂ receptor is expressed in smooth muscle cells, chondrocytes, endothelial and epithelial cells, neutrophils, eosinophils, monocytes, macrophages, dendritic cells, T and B cells (Jutel et al., 2009). The anatomically important uneven distribution of H₂ receptors is described here to allow understanding of the role of histamine through H₂ receptors in the regulation of gastric and neuronal functions.

Molecular cloning of the H₂ receptor (Gantz et al., 1991a,b; Ruat et al., 1991) allowed detection and quantification of receptor mRNA in tissues. In the dog, which was the first species to be analyzed for the H₂ receptor (Gantz et al., 1991b), high expression in the fundus of the stomach and moderate in the brain was reported. In the rat, Northern hybridization analysis has revealed high expression in various parts of the brain, including cerebral cortex, striatum, hippocampus, and hypothalamus. The highest mRNA expression in the rat brain was seen in brain stem (Ruat et al., 1991; Hirschfeld et al., 1992), where several other methods have suggested important physiologic actions. In another quantitative study, the expression in the stomach was reported to be 10-fold higher than that of several brain regions (Karlstedt et al., 2001). Expression in the frontal cortex, striatum, hippocampus, thalamus, hypothalamus, pons, and medulla was rather even, whereas the cerebellum expressed a significantly lower level of mRNA. In situ hybridization showed a much more even distribution than that detected for H₁ receptors and H₃ receptors; although almost all brain areas expressed H₂ receptor mRNA, only a few areas including the piriform cortex, granule cell layer of the dentate gyrus, and hippocampal CA1, CA2, and CA3 showed high density of grains in the forebrain. The red nucleus expresses high levels of H₂ receptor mRNA. In peripheral rat organs, the stomach expresses the highest amounts of H₂ receptor mRNA (Traiffort et al., 1992b).

A detailed account on H₂ receptor mRNA expression in the brain of the guinea pig (Vizuete et al., 1997) as revealed by in situ hybridization suggests widespread distribution in the cerebral cortex, particularly in layers III and V; hippocampal fields CA1, CA2, C3; granular cell layer; and polymorph layer of the dentate gyrus, olfactory bulb, basal ganglia (particularly nucleus accumbens, caudate-putamen, islands of Calleja, olfactory tubercle and ventral pallidum). High expression is also characteristic of the amygdaloid complex, several thalamic, and hypothalamic nuclei. Distribution of H₂ receptor mRNA and receptor radioligand binding in the rat brain are shown in Fig. 5 in comparison with H₁ receptors and H₃ receptors.

In human brain, H₂ receptor radioligand binding is widely distributed with highest densities (measured using [¹²⁵I]iodoaminopotentidine cf. **30**) in the basal ganglia, hippocampus, amygdala, and cerebral cortex (Traiffort et al., 1992b). Lowest densities were detected in cerebellum and hypothalamus. A similar distribution was observed in guinea pig brain (Ruat et al., 1990). In human prefrontal cortex, cells in layer II show higher mRNA expression than the other layers, whereas the H₂ receptor radioligand binding is highest in layers II and III (Jin and Panula, 2005).

In the gastric mucosa, where H₂ receptor antagonists have long been known to exert inhibition of acid secretion, the H₂ receptor localizes to parietal cells of the rat gastric mucosa, in more apical domains than the basal parts where HDC-expressing ECL cells, which are responsible for histaminergic regulation of parietal cell acid secretion, are localized (Panula and Wasowicz, 1993; Diaz et al., 1994). In the brain, H₂ receptor expression and functions are not limited to neurons. There is a significant body of evidence suggesting the presence of H₂ receptors in astrocytes (Kubo et al., 1991; Carman-Krzan and Lipnik-Stangelj, 2000) in vitro and in cultured brain endothelial cells (Karlstedt et al., 1999).

During embryonic development, H₂ receptor mRNA is highly expressed in the rat brain from embryonic day 15 (Karlstedt et al., 2001). Particularly prominent expression is evident in the developing raphe area. From embryonic day 17, strong expression is found in superficial layers of the cortical plate and ventral hypothalamus. It is noteworthy that in rodents there is a distinct transient fetal histaminergic system in the raphe neurons (Auvinen and Panula, 1988; Vanhala et al., 1994), which implies that the fetal expression of H₂ receptor mRNA may be functional during brain development.

Ligand binding methods for H₂ receptors have also been useful to determine H₂ receptor expression. Whereas early studies in guinea pig brain, lung, and transfected CHO cells have been successful using [³H]tiotidine (cf. **31**) (Gajtkowski et al., 1983; Norris et al., 1984; Foreman et al., 1985; Gantz et al., 1991b), studies in rat brain and guinea pig mucosal cells were not successful (Maayani et al., 1982; Batzri and Harmon, 1986). The introduction of [¹²⁵I]iodoaminopotentidine (cf. **30**) was a major step forward, which provides reversible selective high-affinity binding with high sensitivity to membranes of, e.g., brain regions, and a suitable autoradiography radioligand (Hirschfeld et al., 1992). It has high affinity ($K_D = 0.3$ nM) for the H₂ receptor in brain membranes (Martinez-Mir et al., 1990; Ruat et al., 1990; Traiffort et al., 1992a) and transfected cells expressing rat or human H₂ receptors (Traiffort et al., 1992b; Smit et al., 1996a). The compound has also been used for autoradiographic mapping of H₂ receptors in the mammalian brain (Ruat

et al., 1990; Traiffort et al., 1992a; Jin and Panula, 2005). High-affinity binding is detectable in widespread regions of rodent brain. In the guinea pig, high density of binding sites is characteristic of caudate putamen, nucleus accumbens, olfactory tubercle, superficial layers I–III of the cerebral cortex, superficial gray layer of the superior colliculus, and inferior olive. Moderate binding can be found in the deep layers of the cortex, the CA1–CA4 regions of the hippocampus, anterior and lateral nuclear groups of the thalamus, and some hypothalamic nuclei (Ruat et al., 1990). In a detailed mapping study of the ligand binding sites and comparison with mRNA expression in the guinea pig brain, the distribution of binding sites corresponded rather well with the distribution of histaminergic nerve fibers. In human prefrontal cortex H_2 receptor binding is highest in layers II and III, although binding was detectable in all layers, and H_2 receptor mRNA expression is highest in layer II (Jin and Panula, 2005). Discrepancies between RNA and ligand binding patterns corresponded generally to the expected difference in the translation site (cell bodies) and the site of action of the mature receptor protein (dendritic trees of neurons) (Vizuet et al., 1997) (Fig. 8).

D. Function

H_2 receptor activation stimulates the production of cyclic AMP, protein kinase A and the transcription factor cAMP response element-binding protein, which are key regulators of neuronal physiology and plasticity (Haas and Konnerth, 1983; McCormick et al., 1991; Pedarzani and Storm, 1995; Selbach et al., 1997; Atzori et al., 2000). In the CNS, H_2 receptor activation can inhibit nerve cells (Haas and Bucher, 1975), but the most intriguing action is a block of the long-lasting after-hyperpolarization and the accommodation of firing, an effect with a remarkably long duration leading to potentiation of excitation in rodent (Haas and Konnerth, 1983) and human brain (Haas and Panula, 2003) (Fig. 8). A slow excitation is also common (Greene and Haas, 1990), e.g., in oriens-alveus interneurons (Haas et al., 2008), where at the same time, the fast spiking frequency is cut by $K_v3.2$ -containing potassium channel activation (Atzori et al., 2000). A long-lasting potentiation of synaptic transmission in the hippocampus is induced or markedly enhanced (Kostopoulos et al., 1988; Brown et al., 1995; Selbach et al., 1997; Haas and Panula, 2003). An increase of the hyperpolarization-activated inward current I_h (HCN2) opens the door to consciousness by depolarizing thalamic relay neurons (McCormick et al., 1991). A potassium current was blocked through H_2 receptors in olfactory bulb interneurons (Jahn et al., 1995). Furthermore, H_2 receptor activation can inhibit phospholipase A2 and release of arachidonic acid, which likely accounts for opposing physiologic responses elicited by H_1 receptor and H_2 receptor in many tissues (Traiffort et al., 1992b).

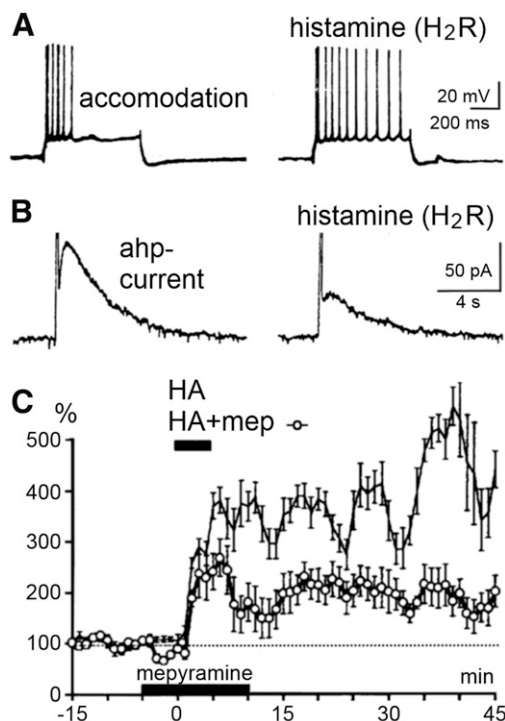


Fig. 8. H_2 receptor and cyclic AMP-mediated potentiation of excitation in rat hippocampal slices. (A) Block of the accommodation of firing in a CA1 pyramidal cell leading to a potentiation of the response to a depolarizing pulse. (B) Block of the I_{AHP} current, which is responsible for a long-lasting Ca^{2+} -dependent afterhyperpolarization and the accommodation of action potential firing. (C) Long-lasting potentiation of glutamatergic synaptic transmission (Schaffer collateral-CA1 pathway). The lower curve (open symbols) illustrates the pure H_2 receptor mediated effect under mepyramine (8), the upper curve illustrates the boosting by H_1 receptor signaling (which is sensitive to Li^+). This long-lasting potentiation (several hours) has the characteristics of the protein kinase A-mediated LLTP (late phase of long-term potentiation) achieved here without high-frequency stimulation. H_1 receptor activation alone causes no potentiation, rather an inhibitory effect presumably through activating a Ca^{2+} -dependent K^+ -current (not shown here) (modified from Selbach et al., 1997).

As most H_2 receptor ligands hardly pass the blood-brain barrier, the behavioral testing of H_2 receptor functions in vivo is difficult, although zolantidine (**29**) may be useful (see section III.E). Mice deficient in H_2 receptor function display cognitive deficits, an impairment in hippocampal long-term potentiation (Dai et al., 2007), and abnormalities in nociception (Mobarakeh et al., 2005, 2006), gastric, and immune functions (Jutel et al., 2001; Teuscher et al., 2004; Schneider et al., 2014a). The suppression of immune responses via the H_2 receptor was not only shown in H_2 receptor-deficient mice but also in human antigen presenting cells, where H_2 receptor stimulation resulted in the downregulation of numerous cytokines (Gutzmer et al., 2005; Glatzer et al., 2013).

E. H_2 Receptor-Selective Ligands

The first agonist with some selectivity for the H_2 receptor was 4(5)-methylhistamine (**17**), which is actually now used as selective H_4 receptor agonist (Durant et al., 1975; Lim et al., 2005) (Fig. 9). Other small molecule ligands used as H_2 receptor agonists

are the aminothiazole derivative amthamine (**18**) (Eriks et al., 1992) and the isothiurea compound dimaprit (**19**), which displays moderate affinity and selectivity (Garbarg et al., 1992). Increased affinity that is higher than that of histamine is found with the longer chained guanidine derivatives arpromidine (**20**) or impromidine (**21**), although both compounds simultaneously display some H₃ receptor antagonist potencies. Whereas impromidine possesses a methylated imidazole ring as with 4-methylhistamine, arpromidine has the fluorinated analogs moiety of the diaryl binding motif of the H₁ receptor antagonist pheniramine (Buschauer, 1989; Leurs et al., 1995a). The homohistamine elements with the guanidine structure on both compounds are mainly

responsible for activation, whereas the other elements are affinity increasing moieties (Dove et al., 2004). In this respect, the chiral forms of sopromidine are sometimes used as helpful pharmacological tools, because the (*R*)-(-) enantiomer sopromidine (**22**) is a potent H₂ receptor agonist, whereas the (*S*)-(+) isoform shows moderate antagonist properties in some assays.

H₂ receptor agonists are not used therapeutically, although arpromidine (**20**) and related imidazolylpropylguanidines were developed as positive inotropic vasodilators for the treatment of severe catecholamine-insensitive congestive heart failure. More recently, aiming at improved drug-like properties, the guanidine group was replaced by an acylguanidine moiety,

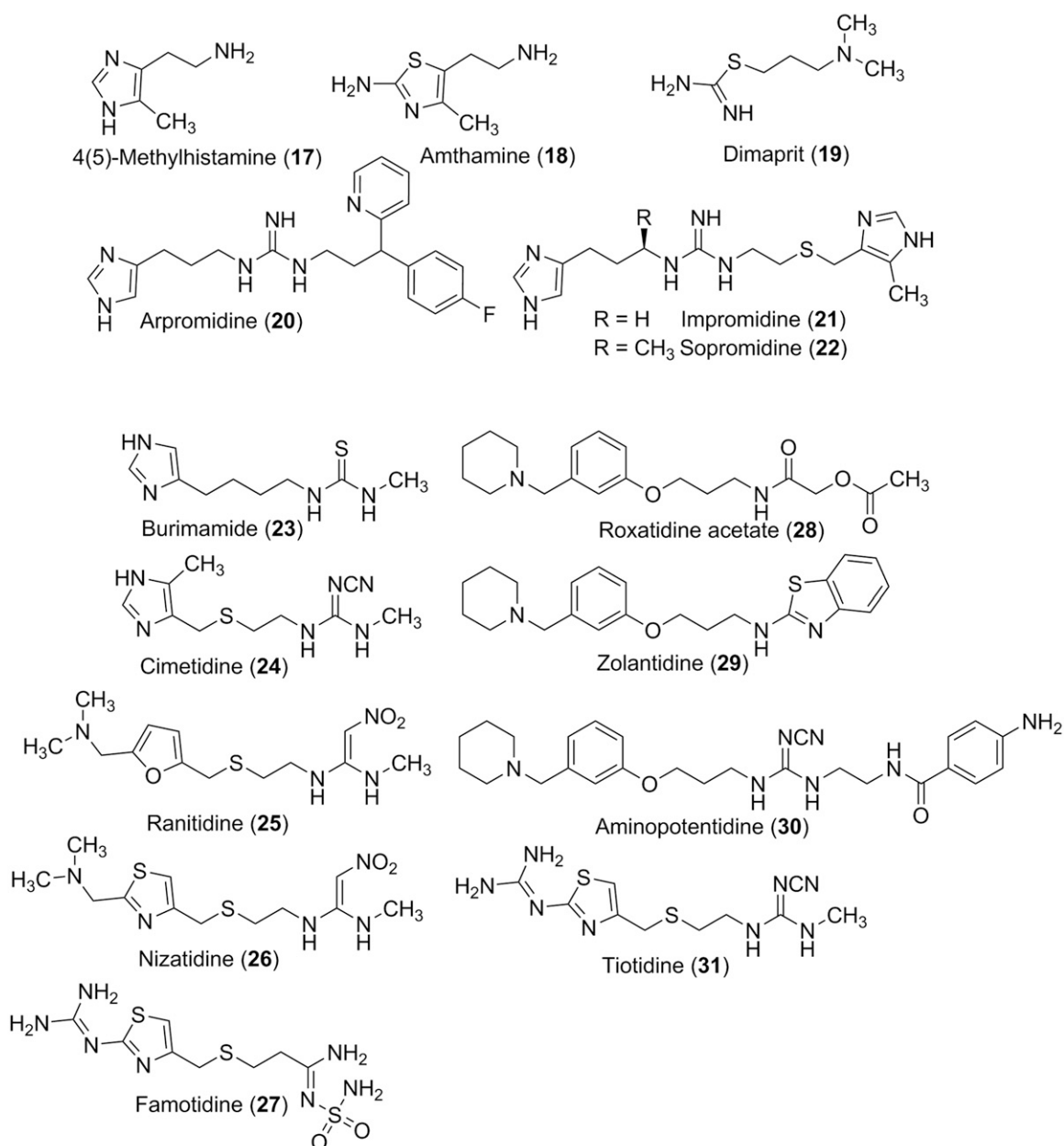


Fig. 9. H₂ receptor ligands.

resulting in substantially reduced basicity (by 4–5 orders of magnitude), but retaining H₂ receptor agonistic activity (Ghorai et al., 2008). Unfortunately, as also found for arpromidine- and impromidine-like compounds, numerous N^G-acylated imidazolylpropylguanidines (e.g., UR-AK24) proved to be poorly selective for the H₂ receptor. Some N-acylguanidines show an overlapping (partial) agonist profile for H₁ and H₂ receptors (Xie et al., 2006). However, many compounds have high affinity for H₃ receptor and H₄ receptor and were, therefore, considered as lead structures in the design of new H₃ receptor and H₄ receptor ligands (see sections IV.D and V.D). Thus, the imidazolylpropylguanidine moiety can be considered a privileged structure for histamine receptor ligands. The selectivity problem was solved by bioisosteric replacement of the imidazol-4-yl with a 2-aminothiazol-5-yl residue, optionally bearing a 4-methyl substituent as in amthamine. 2-Aminothiazoles, such as UR-BIT24, are about equipotent to the corresponding imidazoles at the H₂ receptor but devoid of noteworthy activities at H₁ receptors, H₃ receptors and H₄ receptors (Kraus et al., 2009).

Very recently, the acylguanidine motif was incorporated into bivalent ligands for the H₂ receptor, resulting in the most potent H₂ receptor agonists reported so far (Birnkammer et al., 2012). Searching for potential pharmacological tools to study hypothetical H₂ receptor dimers (Fukushima et al., 1997), two hetarylpropylguanidine moieties were connected by alkanedioyl residues varying in chain lengths (spacer lengths between 6 and 27 Å were covered). Interestingly, the highest potency resided in bivalent ligands with linkers that are, according to the model suggested by Porthoghese (2001) for opioid receptor dimers, too short to allow for simultaneous occupation of the orthosteric binding pockets of both protomers of an H₂ receptor dimer. The optimal distance between the pharmacophoric groups rather suggest binding to the orthosteric and an accessory binding site of the same protomer. In accordance with the structure-activity relationships of monovalent acylguanidines, bivalent ligands comprising one or two imidazole moieties have also remarkably high activities at H₃ receptors and H₄ receptors, whereas homobivalent aminothiazoles are highly selective for the H₂ receptor. The data from the guinea pig H₂ receptor (GTPase assay, GTPγS binding assay) were largely consistent with the results from the isolated guinea pig right atrium. For instance, compounds with a decanedioyl spacer (UR-AK381, UR-AK480, UR-BIT82) were (nearly) full agonists and achieved up to 4000 times the potency of histamine at recombinant human and guinea pig H₂ receptor (Sf9 cell membranes), respectively (Birnkammer et al., 2012) (Fig. 9; Table 1).

The strong relationship of ligand binding areas responsible for receptor (in)activation can also be seen with the first marketed H₂ receptor antagonist cimetidine (**24**) introduced by Sir James Black (Black et al., 1972;

Ganellin, 1981), because this compound with the highly polar cyanoguanidine element is comparable to the affinity increasing element in impromidine (Fig. 2). The reduced basicity of a highly polar core group can also be seen with ranitidine (nitroethendiamine) (**25**), famotidine (**27**) (sulfamoylamidine), roxatidine acetate (amide) (**28**), or the moderately polar compound zolantidine (aminobenzothiazole, **29**), which have poor penetration into the brain with the exception of zolantidine (Baker, 2008). The imidazole moiety of cimetidine has been replaced by other bioisosteric heterocyclic moieties to reduce interaction with CYP3A4 enzymes and to overcome intellectual property issues. Although the H₂ receptor antagonists have been replaced as first regimen therapeutics in peptic ulcer disease by the proton inhibitors, they are still commonly used as safe and reliable therapeutics. Ironically one of the first "selective" H₂ receptor antagonists, the thiourea derivative burimamide (**23**) with low oral bioavailability used in the development of cimetidine, has also been used for the pharmacological characterization of H₃ (antagonist) and H₄ (agonist) receptors because of its affinities and properties at these receptor subtypes.

F. Clinical Pharmacology

The H₂ receptor antagonists cimetidine (the first to be launched by Sir James Black's team in 1977), ranitidine (**25**), nizatidine (**26**), and famotidine (**27**) are well established treatments for patients presenting with dyspepsia, gastric or duodenal ulcers, or gastroesophageal reflux disease (in the United States) (Hershcovici and Fass, 2011; Sigterman et al., 2013). Since the launch of antibiotic therapies for Helicobacter infections (based on the seminal work [Marshall and Warren, 1984; Marshall et al., 1988]) and the discovery of proton pump inhibitors (Olbe et al., 2003), the antisecretory H₂ receptor antagonists are no longer alone at the frontline (with antacids) as symptomatic treatments. Alternating treatment with proton pump inhibitors (the preferred frontline treatment) and H₂ receptor antagonists is used to treat both gastroesophageal reflux disease and more severe refractory reflux disease, e.g., esophageal ulceration or Barrett's esophagus (Hershcovici and Fass, 2011). Treatment with H₂ receptor drugs is generally considered safe and efficacious and is available to large numbers of patients (over the counter in pharmacies for some ligands and as prescription only for others). The symptom suppression elicited by H₂ receptor drugs, however, may mask gastric cancer as has been reported for proton pump inhibitors (Wayman et al., 2000), and the drugs should be used with caution in patients with alarm symptoms. The safety profile, in part, reflects the polar nature of licensed H₂ receptor antagonists, which makes them available in the periphery, but to a lesser extent in the CNS (qualified below). Although H₂ receptor ligands (particularly agonists) have limited selectivity (particularly for H₃/H₄ receptors)

H₂ receptor-activation in the brain mediates important functions (Haas and Konnerth, 1983; Vizuete et al., 1997; Haas and Panula, 2003), and rare reports of CNS toxicity (including depression, confusion, hallucinations) indicate the drugs can enter the brain, particularly in the elderly (Moore and O'Keeffe, 1999), and in patients with renal impairment, although this is often clouded by polypharmacy and concomitant CNS disease. Therapeutic applications for CNS-permeant ligands like zolantidine (**29**) are so far rare, although there is a considerable body of preclinical research highlighting the involvement of H₂ receptors in supraspinal nociception (Nalwalk and Hough, 1995; Nalwalk et al., 1995) and the potential of H₂ receptor antagonists to enhance the effects of opiate analgesics (Mobarakeh et al., 2009) and to exert analgesic effects in models for cholestasis and pruritis (Hasanein, 2011). Further studies have indicated potential utility in psychotic disorders, and in a case report (Kaminsky et al., 1990), a positive therapeutic effect of oral famotidine was reported in a schizophrenic patient. Although one small open-label study (Whiteford et al., 1995) reported no significant effects, two larger studies (Rosse et al., 1990; Deutsch et al., 1993) reported significant therapeutic effects in a group of patients with schizophrenia. A recent randomized double-blind, placebo-controlled study with famotidine in treatment-resistant schizophrenia showed statistically significant improvement in the positive and negative syndrome scale (Meskanen et al., 2013). H₂ receptor agonism blocks accommodation of firing and causes long-term potentiation in hippocampus and cortex (Selbach et al., 1997; Haas and Panula, 2003), which may lead to cognitive enhancement and be worthy of further study.

IV. Histamine H₃ Receptor

Histamine and its receptors were generally known as mediators connected to allergic and inflammatory reactions before the detection of the histamine H₃ receptor in 1983 proved its neglected neurotransmitter function as auto- as well as heteroreceptor at pre- and postsynaptic membranes and revealed its profound influence on different neurotransmitter balances. Although versatile pharmacological tools, localization of H₃ receptor, and influence on brain functions have been described in the early years, the development line was curtailed for a while. Revitalization came from the cloning of the receptor and the detection of nonimidazole antagonists. Actually, the broad potential therapeutic indications due to the multiple neurotransmitter balance influenced by H₃ receptors raise numerous and heterogeneous possibilities in pharmaceutical industry for innovative blockbusters as well as for pipe-dreams.

A. Receptor Structure

The H₃ receptor was first described in 1983 on the basis of pharmacological evidence (Arrang et al., 1983).

Because of the low overall homology of the H₃ receptor with either of the previous cloned H₁ receptors and H₂ receptors, it was not until 1999 that the H₃ receptor cDNA was finally cloned (Lovenberg et al., 1999). Lovenberg and colleagues used a partial cDNA clone (GPCR97) obtained from an Expressed Sequence Tags database that had significant general homology to biogenic amine receptors. The GPCR97 clone was used to probe a human thalamus cDNA library, which resulted in isolation of a full-length clone encoding a putative GPCR. Homology analysis showed the highest homology with M₂ muscarinic acetylcholine receptors and overall low homology with all other biogenic amine receptors. The cDNA encoded an open reading frame of 445 amino acids, which upon heterologous expression was responsive to histamine with an H₃ receptor pharmacological profile. The human H₃ receptor gene has been mapped to chromosome 20q13.33 and is highly expressed in the CNS (Coge et al., 2001a; Tardivel-Lacombe et al., 2001). As with the other members of the histamine receptor family, H₃ receptors are characterized by classic sequence motifs of the family A GPCRs binding biogenic amines. Currently no structural information is available, and all ligand-binding mode hypotheses are based on modeling efforts. Like for all biogenic amine receptors, the H₃ receptor contains the conserved Asp residue in TM3 (Asp114^{3.32}), which is suggested to be involved in the binding of the ethylamine side chain of histamine (Fig. 2) (Kooistra et al., 2013). The binding mode of histamine in a homology model for the H₃ receptor furthermore suggests that the imidazole ring donates a hydrogen bond to E206^{5.46} in TM5, similar to the interaction with Asn198^{5.46} in H₁ receptor. Because the E206^{5.46} can form stronger bonds with the N⁷-nitrogen of histamine than Asn198^{5.46}, this might also explain the substantially higher affinity of histamine for H₃ receptors (and also H₄ receptors; see Fig. 3; Tables 1 and 2) (Kooistra et al., 2013).

After the cloning of the human H₃ receptor, the receptor was cloned in other species through sequence homology screening approaches (Lovenberg et al., 1999; Coge et al., 2001a,b). The rat full-length H₃ receptor was cloned in 2000 (Lovenberg et al., 1999; Liu et al., 2000) followed by guinea pig (Tardivel-Lacombe et al., 2001), mouse (Chen et al., 2002), and monkey H₃ receptor (Yao et al., 2003). The H₃ receptor is approximately 92% conserved between the different species (Hancock et al., 2003). Despite this high conservation, substantial species differences can still sometimes be observed (e.g., Lovenberg et al., 2000).

Rare among GPCRs, the H₃ receptor gene has been reported to consist of either three exons and two introns (Tardivel-Lacombe et al., 2001; Wiedemann et al., 2002) or four exons and three introns (Coge et al., 2001a). The diverse exon/intron junctions result in alternative splice sites producing multiple, distinct

receptor isoforms (Drutel et al., 2001). The existence of multiple human H₃ receptor isoform mRNAs has opened up possible explanations to account for the pharmacological heterogeneity reported in the 1980s and 1990s for the H₃ receptor, within and across species. The reasons for this heterogeneity are complex and still not fully understood. H₃ receptor isoforms have been identified in the rat (Drutel et al., 2001; Morisset et al., 2001), mouse (Rouleau et al., 2004;

Krementsov et al., 2013), and guinea pig (Tardivel-Lacombe et al., 2000).

In all mammalian species tested thus far, the full-length H₃ receptor encodes a polypeptide of 445 amino acids. The 445-amino-acid H₃ receptor is an *N*-linked glycoprotein with a Mr 47,000 (monomeric) and Mr 90,000 (dimeric) based on recombinant H₃ receptor 445 expressed in HEK293 cells and immunoblotting (Bakker et al., 2006). The number of H₃ receptor isoforms possible

TABLE 2
Binding affinities for selected histamine receptor ligands

Compound #	Ligand	<i>h</i> H ₁ R pK _i ^a	<i>h</i> H ₂ R pK _i ^b	<i>h</i> H ₃ R pK _i ^c	<i>h</i> H ₄ R pK _i ^d
1	Histamine	4.6	5.1	8.2	8.1
2	2-(2-Thiazolyl)-ethylamine	5.3			<5
4	Histaprodifen	5.70			<5
6	Diphenhydramine	7.89	5.80	4.60	4.37
8	Mepyramine	8.80	4.63	<5	<5
10	Mizolastine	9.10			<5
11	Levocetirizine	8.15	<6	<6	<4
12	Terfenadine	7.92		<5	<5
13	Fexofenadine	7.54			<5
14	Loratadine	7.21		<5	4.74
15	Desloratadine	8.40	6.45 ^e	<5	5.10
17	4(5)-Methylhistamine	<5	5.10	4.72	7.73
18	Amthamine		6.82		5.30
19	Dimaprit	<5	4.60	6.08	6.42
20	Arpromidine	6.5	6.3-8.0		
21	Impromidine	5.2	7.64	6.99	7.76
23	Burimamide	4.3 ^f	5.41	7.36	6.97
24	Cimetidine	4.75	5.84	4.69	5.03
25	Ranitidine	4.47	6.67	4.89	<5
27	Famotidine	<5 ^e	7.56		<5
30	Aminopotentidine	4.60	7.40	7.10	<5
31	Tiotidine	<4	7.77	<4 ^f	<5
32	<i>N</i> α-Methylhistamine	4.20	4.30	9.00	7.13
33	(<i>R</i>)-α-Methylhistamine	<5	<4	8.6	6.76
34	Imetit	4.30	5.10	9.29	8.48
35	Immepip	4.79	<3.5	9.44	7.79
36	Methimzepip			9.00	5.70
38	Proxyfan			8.2	7.30
40	Thioperamide	3.88	4.27	7.6	7.04
41	Clobenpropit	5.45	5.47	9.0	7.98
42	Ciproxifan	<5	<5	7.1	5.73
45	Pitolisant	5.78	4.96	8.06	<4
48	Conessine	<5	<5	8.3	<5
55	MK-0249	<5	<5	8.2	<5
56	Clozapine	8.65	6.82	<4	6.26
58	JNJ-7777120	<5	<6	5.30	8.09
67	ZPL-389378			6.73	8.31
72	JNJ-39758979	<6	<6	6.0	7.9
74	INCB-38579	<5	<5.3	6.39	8.3
75	ST-1006	<6	<6	6.29	7.9

^aData from Tran et al. (1978); Chang et al. (1979); Kanba and Richelson (1984); De Backer et al. (1993); Leurs et al. (1994a); Vollinga et al. (1994). Sharif et al. (1996); Merlos et al. (1997); Bakker et al. (2001); Gillard et al. (2002a); Esbenshade et al. (2003); Govoni et al. (2003); Thurmond et al. (2004, 2014a,b); Bielory et al. (2005); Xie et al. (2006); Ligneau et al. (2007); Nagase et al. (2008); Zhao et al. (2008); Sander et al. (2009); Rossbach et al. (2011); Appl et al. (2012); Shin et al. (2012); Savall et al. (2014); Where multiple values are reported, they have mostly been averaged.

^bData from Harada et al. (1983); Gantz et al. (1991b); Leurs et al. (1994a, 1995b); Sharif et al. (1996); Kreutner et al. (2000); Saitoh et al. (2002); Esbenshade et al. (2003); Thurmond et al. (2004, 2014a,b); Bielory et al. (2005); Lim et al. (2005); Xie et al. (2006); Preuss et al. (2007); Nagase et al. (2008); Zhao et al. (2008); Sander et al. (2009); Rossbach et al. (2011); Shin et al. (2012); Savall et al. (2014); and Levocetirizine New Drug Application #22-064; Loratadine New Drug Application #21-165. Where multiple values are reported, they have mostly been averaged.

^cData from West et al. (1990); Vollinga et al. (1994); Sharif et al. (1996); Kato et al. (1997); Lovenberg et al. (1999); Ligneau et al. (2000, 2007); Coge et al. (2001b); Liu et al. (2001a); Wieland et al. (2001); O'Reilly et al. (2002); Wellendorph et al. (2002); Wulff et al. (2002); Esbenshade et al. (2003); Thurmond et al. (2004, 2014a,b); Bielory et al. (2005); Lim et al. (2005); Gbahou et al. (2006); Nagase et al. (2008); Zhao et al. (2008); Sander et al. (2009); Mowbray et al. (2011); Rossbach et al. (2011); Appl et al. (2012); Shin et al. (2012); Andaloussi et al. (2013); Savall et al. (2014); and Levocetirizine New Drug Application #22-064. Where multiple values are reported, they have mostly been averaged.

^dData from Ligneau et al., 2000; Liu et al., 2001b; Morse et al., 2001; Zhu et al., 2001; O'Reilly et al., 2002; Esbenshade et al., 2003; Thurmond et al., 2004, 2014a,b; Lim et al., 2005; Gbahou et al., 2006; Ligneau et al., 2007; Nagase et al., 2008; Zhao et al., 2008; Deml et al., 2009; Sander et al., 2009; Mowbray et al., 2011; Rossbach et al., 2011; Appl et al., 2012; Shin et al., 2012; Andaloussi et al., 2013; Savall et al., 2014. Where multiple values are reported, they have mostly been averaged.

^eGuinea pig.

^fRat.

is high because of simultaneous occurrence of multiple splicing events in the same H₃ receptor mRNA. The mechanisms regulating alternative splicing of the H₃ receptor gene remain to be investigated.

Approximately 20 shorter human isoforms have been identified to date with deletions in the N terminus, second TM domain, and first extracellular loop, intracellular loop or at the C terminus (regions A–D; see Fig. 10). (Leurs et al., 2005). Alternative splicing in regions A (red) and/or B (orange) results in partial deletion of the N-terminal domain and/or TM2 and EL1, respectively (not shown). Such splicing events will result in nonfunctional GPCR isoforms. In contrast, distinct splice events in region C (green) results in an IL3 (intracellular loop 3) of variable length and/or deletion of TM5, -6, and/or -7. Alternative splicing in region D (blue) adds eight additional residues to the C-terminal tail of H₃ receptors. Finally, a frameshift after residue 171 results in a truncated receptor protein (magenta) (Leurs et al., 2005). Isoforms that have deletions in their third intracellular loop have attracted significant interest because of the coupling of the third intracellular loop with G proteins (Drutel et al., 2001). These isoforms show variation in their pharmacological profile (Hancock et al., 2003), such as agonist potencies, signaling properties and expression patterns (Drutel et al., 2001), and constitutive activity (Morisset et al., 2001; Bongers et al., 2007b).

Regional topographical differences for the isoform mRNAs has given rise to speculation that H₃ receptor heterogeneity could underlie different activities and functions of the H₃ receptor in specific brain regions (Coge et al., 2001a; Drutel et al., 2001). Furthermore, there is growing evidence that homo- and hetero-

oligomerization of H₃ receptor isoforms occur and yield a novel regulatory mechanism (Bakker, 2004). Not all of the isoforms are likely to be expressed at the surface as a receptor, e.g., rat isoforms H_{3D}, H_{3E}, and H_{3F}. These isoforms have been shown to act as dominant negatives in vitro to either directly or indirectly control surface expression of the rat isoforms H_{3A}, H_{3B}, and H_{3C} (Bakker et al., 2006). Differential and overlapping expression of rodent H₃ receptor isoforms has been reported (Drutel et al., 2001). Immortalized rat brain vascular endothelial cells express both the full-length isoform H_{3A} and H_{3C} (Karlstedt et al., 2013). Previously, Coge et al. (2001a) had shown two human isoforms that varied from the full length in terms of binding and signal transduction. To determine the biologic role of the different isoforms, the pharmacological properties of the human H₃ receptor₄₃₁ and the human H₃ receptor₃₆₅ were compared with the full-length human H₃ receptor₄₄₅. The human H₃ receptor₄₃₁ was unable to bind [¹²⁵I]iodoproxyfan because of a deletion in the second transmembrane. More recently, Bongers et al. (2007b) reported, based on mRNA levels, differential expression of the human H₃ receptor₃₆₅ and the human H₃ receptor₄₄₅, with the human H₃ receptor₃₆₅ displaying higher expression levels than the human H₃ receptor₄₄₅ in many brain structures. The human H₃ receptor₃₆₅ also displayed higher affinity and potency for H₃ receptor agonists and conversely a lower potency and affinity for H₃ receptor inverse agonists. The human H₃ receptor₃₆₅ also displayed higher constitutive signaling compared with the human H₃ receptor₄₄₅ in both [³⁵S]GTPγS binding and cAMP functional assays. Lower expression patterns were observed for the human H₃ receptor₄₁₅, human H₃ receptor₄₁₃, and human H₃ receptor₃₂₉, which

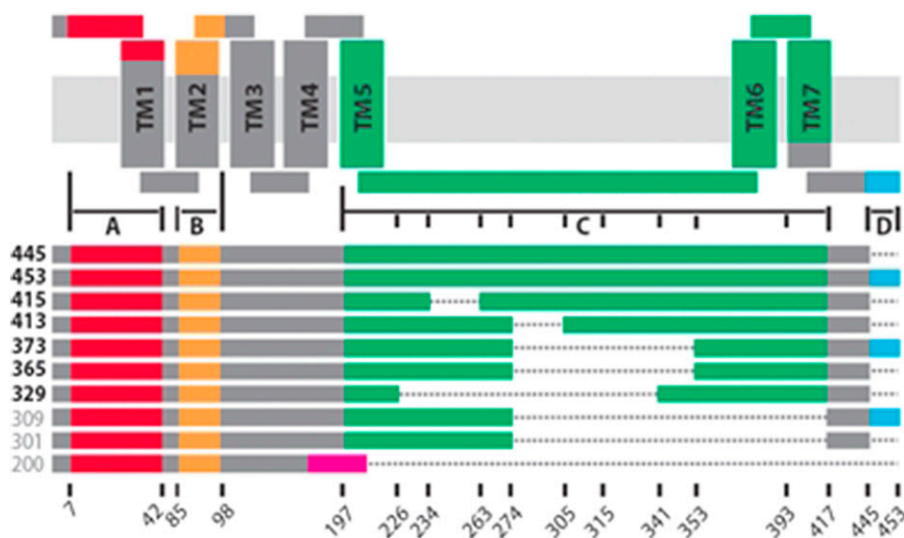


Fig. 10. Schematic overview of several 7TM and truncated H₃ receptor isoforms. Alternative splicing in regions A (red) and/or B (orange) results in partial deletion of the N-terminal domain and/or TM2 and EL1, respectively (isoforms not shown). Distinct splice events in region C (green) results in an IL3 of variable length and/or deletion of TM5, -6, and/or -7. Alternative splicing in region D (blue) adds 8 additional residues to the C-terminal tail of H₃R. Finally, a frameshift after residue 171 results in a truncated receptor protein (magenta). Truncated H₃ receptor isoforms are indicated in gray.

also bind H₃ receptor ligands and exhibit subtle differences in coupling to signaling mechanisms. Protein expression of the various human isoforms in brain tissue awaits confirmation and encourages the development of isoform-selective antibodies.

Genetic polymorphisms have also been identified within the human H₃ receptor gene, which may further contribute to the wide diversity of the H₃ receptor pharmacology. Independent publications and GenBank submissions of the human H₃ receptor sequences have either a glutamic acid or aspartic acid at position 19 (Hancock et al., 2003). Another polymorphism has been identified at position 280 (IL3), an alanine to valine substitution in a patient suffering with Shy-Drager syndrome, which is also known as neurologic orthostatic hypotension, a disease characterized by neuronal degeneration and autonomic failure. Abbott Laboratories (Abbott Park, IL) confirmed this finding as well as another polymorphism at position 197, a tyrosine to a cysteine substitution (Hancock et al., 2003). Several single amino acid polymorphisms have also been identified in the third intracellular loop in rat H₃ receptors (Coge et al., 2001a). Similarly, polymorphic sites are thought to be present in the mouse H₃ receptors because complete sequences do not match partial sequences (Goodearl et al., 1999). For most of the reported polymorphisms no functional data are available. Yet expression of the Shy-Drager syndrome linked Ala280Val H₃ receptor mutant on CHO-K1 cells showed that this mutant receptor showed reduced signaling efficacy in both cAMP signaling and [³⁵S]GTPγS assays (Flores-Clemente et al., 2013).

B. Signal Transduction Mechanisms

The H₃ receptor mediates pertussis toxin-sensitive [³⁵S]GTPγS binding in rat cerebral cortex membranes (Clark and Hill, 1996) and a variety of other brain areas and transfected cells (Rouleau et al., 2002; Bongers et al., 2007b). In addition, pertussis toxin-sensitive inhibition of N-type Ca²⁺ channels has been reported in human and guinea pig heart (for previous review, see Bongers et al., 2007a). These data point to the H₃ receptor being a G_i/G_o protein-coupled receptor. In agreement with this concept, the human and rat H₃ receptors recombinantly expressed in, e.g., SK-N-MC neuroblastoma cells, are negatively coupled to cAMP accumulation (Lovenberg et al., 1999, 2000). The human H₃ receptor and rat H₃ receptor expressed in Sf9 insect cells couple equally well to G_{i1}, G_{i2}, G_{i3}, and G_{o1} as assessed by measurement of steady-state GTPase activity upon H₃ receptor/G protein coexpression (Schnell et al., 2010).

Activation of G_{i/o} proteins by H₃ receptors also results in the activation of mitogen-activated protein kinase (MAPK) pathways (Drutel et al., 2001; Giovannini et al., 2003). Using rat H₃ receptor isoforms with different IL3 loops transiently expressed in COS-7

cells, Drutel et al. (2001) showed that H₃ receptor agonists stimulate MAPK phosphorylation in a pertussis toxin-sensitive manner. Interestingly, the long (445-amino-acid) isoform H_{3A} coupled considerably better to MAPK phosphorylation compared with the shorter H_{3B} and H_{3C} isoforms (Drutel et al., 2001). In contrast, the rat H₃ receptor isoforms with deletions in the third intracellular loop were more effective to activate cAMP-responsive element-dependent transcription, compared with the full-length H_{3A} receptor (Drutel et al., 2001). MAPK activation after H₃ receptor activation is not restricted to recombinant systems but has also been observed in native tissue (Giovannini et al., 2003). In rat hippocampal CA3 cells MAPK activation via H₃ receptor has been linked to memory improvement (Hill et al., 1997). Similarly, G_{i/o} activation via H₃ receptors can activate PI3K, leading to the subsequent activation and phosphorylation of protein kinase B (also known as Akt). Activated protein kinase B subsequently phosphorylates and thereby inhibits the action of glycogen synthase kinase 3-β, a major tau kinase in the brain (Bongers et al., 2007c) linked to several diseases, e.g., Alzheimer's disease.

Other pathways modulated by the H₃ receptor include G_{16α}-mediated increase in cytosolic calcium ion concentration (Krueger et al., 2005), inhibition of histamine synthesis and release (Torrent et al., 2005; Moreno-Delgado et al., 2006), decrease of the cytosolic Ca²⁺ concentration in sympathetic nerve endings (Silver et al., 2001, 2002), and inhibition of Na⁺/H⁺ exchange activity (Silver et al., 2001).

In addition to agonist-induced signaling, the H₃ receptor also signals in an agonist-independent, constitutive manner, thereby being one of the few GPCRs for which constitutive signaling has been observed in vivo. Both the rat H₃ receptor and human H₃ receptor exhibit high constitutive activity, resulting in high basal GTPγS binding (Morisset et al., 2000; Rouleau et al., 2002). The high basal GTPγS binding is inhibited by inverse agonists such as thioperamide and ciproxifan. Moreover, constitutive activity of the H₃ receptor results in inhibition of forskolin-stimulated cAMP accumulation in recombinant systems, agonists further decreasing cAMP accumulation, and inverse agonists enhancing cAMP accumulation (Wieland et al., 2001). Moreover, constitutive H₃ receptor activation leads to increased arachidonic acid release and inhibition of neurotransmitter release in vivo (Morisset et al., 2000; Rouleau et al., 2002).

Like the other histamine receptors, H₃ receptors are able to form homo- and heterodimers (Panula and Nuutinen, 2013). Whereas the biochemical evidence seems to indicate that the H₃ receptor isoforms can form homo- and heterodimers, the direct relevance for signaling or functional responses has not been elucidated. Behavioral and signaling studies have provided more conclusive evidence that H₃ receptor can form

functional heterodimers with dopamine receptors (Ferrada et al., 2008, 2009). Activation of H₃ receptors inhibits D₁ receptor agonist SKF-81297-induced cAMP accumulation in slices of striatum (Sanchez-Lemus and Arias-Montano, 2004) and inhibits D₁ receptor-dependent release of [³H]GABA from rat striatum (Arias-Montano et al., 2001). Furthermore, in transfected cells, H₃ receptor or D₁ receptor signaling can be blocked not only by the selective respective antagonist but also by a selective antagonist of the partner receptor (Ferrada et al., 2009), and H₃ receptor or D₁ receptor antagonists can block MAPK signaling induced by H₃ receptor or D₁ receptor agonists (Moreno et al., 2011) in the brain. In this context, it is interesting that histaminergic neurons, which project to the striatum, contain dopa-decarboxylase and can produce dopamine after uptake of dopa that can be released from nearby dopaminergic neurons or is available in patients treated with L-dopa for Parkinson's disease (see Yanovsky et al., 2011).

C. Anatomic Framework

Cloning of the H₃ receptor in 1999 allowed verification of the high expression of the receptor in the brain (Lovenberg et al., 1999). This first report also established that the H₃ receptor is abundantly expressed in very important areas of the brain (Fig. 5), e.g., cerebral cortex, thalamus, caudate putamen, ventromedial nucleus of the hypothalamus, and several aminergic projection systems, including histaminergic tuberomammillary nucleus (TMN) neurons and the noradrenergic neurons of locus coeruleus. Subsequently, detailed analyses of H₃ receptor mRNA expression in rat brain (Pillot et al., 2002b) and findings on differential expression of the H₃ receptor isoforms (Drutel et al., 2001) have further contributed to the current understanding that the H₃ receptor plays important roles in multiple functions in the CNS. In the cerebral cortex of the rat, intense labeling in situ hybridization samples was characteristic of layers V in most cortical areas and in layer III (particularly in the secondary motor cortex), granular layer IV of the auditory cortex, and layer VI of the somatosensory and auditory cortices (Pillot et al., 2002a). Expression of the different splice forms in the rat brain shows differences that may be functionally significant: there are differences in expression patterns at least in the cerebral cortex, hippocampus, and cerebellum (Drutel et al., 2001). The distribution of H₃ receptor mRNA and ligand binding in comparison with the H₁ and H₂ receptor are shown in Fig. 5.

In human brain, the expression of H₃ receptor mRNA in the prefrontal cortex is higher in layer V than in any other layer in Brodmann's areas 8–11, 24, 32, 44, 45, 46, and 47, i.e., in almost all areas investigated (Jin and Panula, 2005). In contrast, the [³H]N^α-methylhistamine binding in the same samples is highest in layers III and IV, suggesting that most of the receptors occur either on the dendrites of the

pyramidal neurons or in the thalamocortical axons. The lowest binding density is seen in the superficial layer I and deep layer VI (Jin and Panula, 2005).

H₃ receptor mRNA is expressed at a high intensity in the human dorsal thalamus, the only part of thalamus that projects to the cortex. High to moderate expression is found in most of the principle relay nuclei (anterior, lateral, and medial nuclei, lateral geniculate nucleus), midline, and internal medullary laminar nuclei, whereas the expression level is low in the medial geniculate nucleus, posterior thalamic region (pulvinar), and the ventral thalamus (reticular nucleus, zona incerta). The expression is particularly abundant in the associate relay areas that project to the prefrontal cortex, notably the mediodorsal thalamic nucleus (Jin et al., 2002). H₃ receptor binding sites are detectable using [³H]N^α-methylhistamine also in human thalamus (Jin et al., 2002). The highest density of binding sites was seen in the midline nuclei (reuniens, paraventricular, subhabenula), mediodorsal nucleus, some of the internal medullary laminar nuclei (parafascicular, paratenial, fasciculosus), and parts of the pulvinar (medial, inferior, diffuse). The binding level is generally low in other parts of the thalamus. This distribution is in agreement with the concept that thalamic neurons, which express H₃ receptors, project to the cortex, where radioligand binding is detected on presynaptic terminals.

In the basal ganglia, H₃ receptor mRNA signal intensity is observed in decreasing order in the following structures: putamen > frontal cortex > globus pallidus externum > globus pallidus internum (Anichtchik et al., 2001). In the mesencephalon (at the level of the superior colliculus), in substantia nigra, H₃ receptor mRNA in situ signal is very low or undetectable, whereas a specific signal is observed in the red nucleus. In the corpus striatum, the highest expression of H₃ receptor mRNA is detected in the putamen, whereas in the paleostriatum the expression is low and barely higher than the nonspecific background (Anichtchik et al., 2001). In normal human brain, the H₃ receptor radioligand binding level is found in decreasing order: substantia nigra > putamen > globus pallidus externus > globus pallidus internus > frontal cortex (Anichtchik et al., 2001). This distribution suggests that the striatonigral projection neurons express H₃ receptors, which is likely to regulate the release of GABA within the substantia nigra. No evidence for expression of H₃ receptors in human dopaminergic nigral neurons was found in one study (Anichtchik et al., 2001). In Parkinson's disease, H₃ receptor mRNA expression in the pallidum externum is elevated compared with the normal brains. In Parkinson's disease substantia nigra, an increase of the receptor binding density has been detected (Anichtchik et al., 2001). This increase in receptor binding coincides with a clear increase in histamine content (Rinne et al., 2002) and histamine-immunoreactive nerve fibers (Anichtchik et al., 2000) in

substantia nigra, suggesting that either the disease process itself, e.g., through an effect of decreased dopamine or associated medication, modifies the histaminergic system.

During embryonic development, the H₃ receptor is expressed early (from embryonic days 14 and 15 onward) in the CNS of the rat (Heron et al., 2001; Karlstedt et al., 2003). The expression is prominent in the midbrain ventricular epithelium, in medulla oblongata, and spinal cord, which suggests developmental roles for H₃ receptors, and in brown fat, which suggests a role in energy metabolism or development of these cells (Karlstedt et al., 2003). In another study, which used cRNA probes instead of an oligonucleotide probe, a more widespread distribution of H₃ receptor mRNA in developing rat tissues was observed, with significant signals in spinal ganglia, salivary glands, respiratory epithelium, gastric and intestinal mucosa, skin, thymus, liver, heart, and kidney (Heron et al., 2001). This widespread distribution indicates that during development, H₃ receptor functions may extend well beyond the nervous system.

Antibodies have been generated against synthetic peptides from the human and rat H₃ receptors to localize the receptor protein in mammalian tissues. One of these antibodies detects immunoreactive species at 62 and 93 kDa in mouse brain (Chazot et al., 2001). Immunoreactivity was localized in pyramidal neurons of lamina V of the rodent cerebral cortex and in medium-sized neurons in the striatum, cerebellar Purkinje cells, and the pyramidal cell layer of the hippocampus (Chazot et al., 2001). The H₃ receptor mRNA distribution in rat (Pillot et al., 2002a) and human (Jin and Panula, 2005) cortex is mainly in deep laminae, whereas the receptor radioligand binding is more even (Pillot et al., 2002a; Jin and Panula, 2005). The receptor immunoreactivity could be expected in the same areas as radioligand binding, which motivates further studies using parallel immunocytochemistry with in situ hybridization and/or radioligand binding analysis to verify the results. In adult rat stomach, the H₃ receptor is found in ECL cells, which also express HDC (Grandi et al., 2008). In the sensory system of the rat and mouse, H₃ receptor immunoreactivity resides in large A δ fibers that terminate in Meissner's corpuscles surrounded hair follicles (Cannon et al., 2007). In dorsal root ganglia, H₃ receptor immunoreactivity was localized in medium-sized and large cells, which also expressed calcitonin gene-related peptide; H₃ receptor KO mice did not show this expression, suggesting selectivity of labeling. The localization suggests that H₃ receptor containing fibers are involved in high-threshold mechanical nociception. Epidermal Merkel cells and keratinocytes also express H₃ receptor-like immunoreactivity. In the locus coeruleus, histamine activates, through H₂ receptors,

noradrenergic neurons that inhibit neuropathic pain. This descending inhibition may be facilitated through blocking the H₃ receptor-mediated autoinhibition of histaminergic terminals in the locus coeruleus (Wei et al., 2014).

Although presence of the H₃ receptor in rodent sensory ganglia on a subset of A δ fibers and lack of reactivity in H₃ receptor KO mice has been shown using immunocytochemistry (Cannon et al., 2007), H₃ receptor expression in peripheral ganglia using in situ hybridization has not been systematically analyzed. Particularly many commercial antibodies against the H₃ receptor are nonspecific: they detect multiple unrecognized bands in Western blot analysis and also react in tissues of H₃ receptor KO mice. Thus the specific neuronal phenotypes in autonomous and sensory ganglia that express H₃ receptors are still unknown in most cases.

The apparent high affinity of (*R*)- α -methylhistamine (**33**) for the H₃ receptor has enabled the use of this compound as a radiolabeled probe (Arrang et al., 1987b). This compound has been successfully used to identify a single binding site in rat cerebral cortical membranes, which in phosphate buffer has the pharmacological characteristics of the H₃ receptor (Arrang et al., 1987b, 1990). [³H](*R*)- α -Methylhistamine binds with high affinity ($K_D = 0.3$ nM) to rat brain membranes, although the binding capacity is generally low (approximately 30 fmol/mg protein; Arrang et al., 1987b). It should be noted that this ligand has a moderate affinity for the H₄ receptor (Liu et al., 2001b), and so the anatomic profile may be incomplete.

Radiolabeled H₃ receptor antagonists have been available since the early 1990s. The first compound to be developed was [¹²⁵I]iodophenpropit, which has been used to successfully label H₃ receptors in rat brain membranes (Jansen et al., 1992). Inhibition curves for thioperamide and iodophenpropit were consistent with interaction with a single binding site, but H₃ receptor agonists were able to discriminate high [4 nM for (*R*)- α -methylhistamine]- and low [0.2 mM for (*R*)- α -methylhistamine]-affinity binding sites (Jansen et al., 1992). More recently, [³H]GR16820 (Brown et al., 1994) and [¹²⁵I]iodoproxyfan (Ligneau et al., 1994) have also proved useful as high-affinity radiolabeled H₃ receptor antagonists. [¹²⁵I]iodoproxyfan (Stark et al., 1996) is the most potent and selective ligand available at the present time, with a K_D of 65 pM (Ligneau et al., 1994). In rat striatum, in the presence of guanine nucleotides such as guanosine (3-thiotriphosphate) (GTP γ S), 40% of the binding sites exhibited a 40-fold lower affinity for H₃ receptor agonists, providing further evidence for a potential linkage of the H₃ receptor to G proteins (Ligneau et al., 1994). [³H]Thioperamide and [³H]5-methylthioperamide have also been used to label H₃ receptors in rat brain membranes (Yanai et al., 1994; Alves-Rodrigues et al.,

1996). However, [^3H]thioperamide (**40**) binds additionally to low-affinity, high-capacity, non- H_3 receptor sites in this tissue (Alves-Rodrigues et al., 1996) and acts as a ligand for H_4 receptors (Gbahou et al., 2006). Meanwhile different potent fluorescent H_3 receptor antagonists have been developed that can be used for imaging purposes (Amon et al., 2006, 2007).

[^{35}S]GTP γ S binding assays can be used to detect receptor-dependent activation of G proteins (Wieland et al., 1994). This method can be used to locate anatomic patterns of G protein activation in tissues. In the rat brain, the histamine stimulated [^{35}S]GTP γ S binding corresponds to the H_3 receptor radioligand binding pattern and responds to H_3 receptor antagonists, suggesting that histamine-induced signals are due to activation of H_3 receptors (Laitinen and Jokinen, 1998). By using this method, it has been shown that in hibernating ground squirrels the H_3 receptors, which are upregulated in caudate putamen during hibernation bout, can be activated throughout the hibernation cycle (Sallmen et al., 2003a). This, together with the increased histamine turnover during hibernation (Sallmen et al., 1999), indicates that histamine may be a critical factor in maintaining the hibernation state.

In addition to data obtained from ligand binding and [^{35}S]GTP γ S binding studies, evidence for the localization of H_3 receptors has also come from functional studies involving inhibition of neurotransmitter release and electrophysiology. The histaminergic neurons located in the tuberomammillary nucleus of the posterior hypothalamus project throughout the central nervous system. Histamine production and release is under feedback control through autoreceptors (H_3 receptors); however, a large number of nonhistaminergic neurons, including their axon varicosities, carry H_3 heteroreceptors. This makes the prediction of H_3 receptor-mediated effects difficult but opens up an avenue to multiple interference with neural functions (Fig. 11).

Candidate drugs as clinical PET tracers to both study the H_3 receptor system and measure receptor occupancy of H_3 receptor therapeutic compounds have been developed (Selivanova et al., 2010). [^{11}C](1*R*,40*R*)-5-Methoxy-*N*-methyl-3-oxo-*N*-(2-piperidin-1-ylethyl)-3*H*-spiro[2-benzofuran-1,10-cyclohexane]-40-carboxamide and [^{18}F](1*R*,40*R*)-5-(fluorodideuteromethoxy)-*N*-methyl-3-oxo-*N*-(2-piperidin-1-ylethyl)-3*H*-spiro[2-benzofuran-1,10-cyclohexane]-40-carboxamide bind specifically to sections of rhesus monkey and human brain, where substantia nigra, nucleus accumbens, and globus pallidus show strong signals. PET imaging on rhesus monkey brain shows strong signals in the striatum and frontal cortex and lower signals in the cerebellum (Hamill et al., 2009).

D. Function

The H_3 receptor was first characterized as an autoreceptor regulating histamine synthesis and release from rat cerebral cortex, striatum, and hippocampus

(Arrang et al., 1985a,b, 1987a, 1988a). H_3 receptor-mediated inhibition of histamine release has also been observed in human cerebral cortex (Arrang et al., 1988b). Differences in the distribution of H_3 receptor binding sites and the levels of histidine decarboxylase (an index of histaminergic nerve terminals) suggested at an early stage that H_3 receptors were not confined to histamine-containing neurons within the mammalian CNS (Arrang et al., 1987a; van der Werf and Timmerman, 1989). This has been confirmed by the observations that H_3 receptors can regulate serotonergic (Schlicker et al., 1988, 1989; Threlfell et al., 2004), noradrenergic (Schlicker et al., 1989), cholinergic (Clapham and Kilpatrick, 1992), and dopaminergic (Schlicker et al., 1992, 1993; Munari et al., 2013) neurotransmitter release in mammalian brain. H_3 receptor activation inhibits the firing of the histamine neurons in the posterior hypothalamus through a mechanism distinct from autoreceptor functions found on other aminergic nuclei, namely a block of Ca^{2+} -current, which is part of the pacemaker cycle in histaminergic neurons (Stevens et al., 2001) (Fig. 12). Electrophysiological evidence for reduction of excitatory transmitter release (glutamate) has been presented by Brown et al. (Brown and Reymann, 1996; Brown and Haas, 1999). Activation of H_3 receptors inhibits neurotransmission also in the peripheral autonomous and sensory systems. Sympathetic neurotransmitter release is regulated by H_3 receptor in guinea pig mesenteric artery (Ishikawa and Sperelakis, 1987), human saphenous vein (Molderings et al., 1992), guinea pig atria (Endou et al., 1994), human heart (Imamura et al., 1996), rat tail artery (Godlewski et al., 1997), and dog kidney (Yamasaki et al., 2001). Neuropeptide (tachykinins or calcitonin gene-related peptide) release from sensory C fibers from airways (Ichinose and Barnes, 1990), meninges (Matsubara et al.,

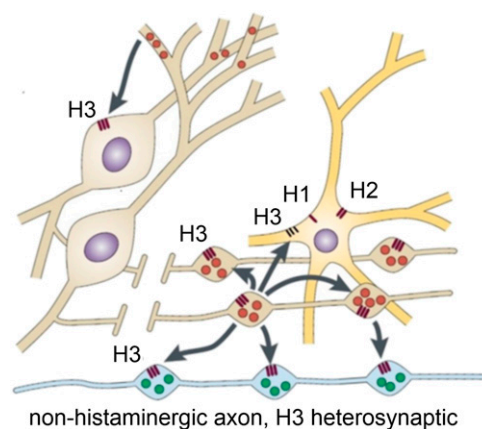


Fig. 11. Neuronal targets of histaminergic neurons. H_1 receptor and H_2 receptor are located on many neurons where they modulate the activity in several ways (see text). H_3 receptors are located on histaminergic neuron somata, dendrites, and axons to control firing, histamine synthesis, and release acting as autoreceptors. As heteroreceptors they control transmitter release from a wide variety of nonhistaminergic axons and in some cases inhibit the activity of nonhistaminergic neurons. Modified from Haas and Panula (2003).

1992), skin (Ohkubo and Shibata, 1995), heart (Imamura et al., 1996), and rat mesenteric arteries (Sun et al., 2011) is also controlled by H₃ receptors. A modulation of acetylcholine, capsaicin, and substance P effects by H₃ receptors in isolated perfused rabbit lungs has also been reported (Delaunois et al., 1995).

H₃ receptor mRNA expression and G protein activation is increased in the basal ganglia of hibernating mammals during the hibernation period (Sallmen et al., 2003a) along with histamine levels and turnover (Sallmen et al., 1999), which suggests that histamine may be involved in regulation of hibernation or arousal from the bout. Indeed, infusion of histamine in the hippocampus of golden-mantled ground squirrel causes a delayed arousal (Sallmen et al., 2003b).

As autoreceptors on somata, dendrites, and axons of TMN neurons, constitutively active H₃ receptors (Arrang et al., 2007) inhibit cell firing (Stevens et al., 2001), as well as histamine synthesis and release from varicosities (Arrang et al., 1983; Torrent et al., 2005; Moreno-Delgado et al., 2006). This autoinhibition by H₃ receptor agonists [e.g., (*R*)- α -methylhistamine; **33**] and its removal by H₃ receptor antagonists/partial agonists can be demonstrated in recordings from TMN neurons. As presynaptic heteroreceptors, H₃ receptors control the release of several other transmitters, including biogenic amines (Schlicker et al., 1994, 1999), acetylcholine (Blandina et al., 1996; Arrang, 2007), GABA (Jang et al., 2001), and glutamate; field potentials evoked by stimulation of glutamate fiber bundles, e.g., in hippocampus or striatum, show a marked decrease in the presence of an H₃ receptor agonist (Brown and Haas, 1999; Doreulee et al., 2001) (Fig. 12). In this context, the H₃ receptor has been shown as a potential therapeutic target for cerebral ischemia (Yan et al., 2014). Heterogeneity of the histaminergic neurons with respect to function and

projections has been demonstrated by Giannoni et al. (2009); activation of histaminergic neurons by blocking the somatic autoreceptors causes differential release of histamine measured by microdialysis in different target regions of rats; cortex and nucleus basalis display strong increases of histamine release, but both the ventral and the dorsal striatum, regions receiving ample innervation too, do not show any such release (Blandina et al., 2012). H₃ autoreceptors may thus have been absent, or not activated, in the histaminergic neurons projecting to these latter regions.

H₃ receptor KO mice display changes in behavioral states, reduced locomotion (Toyota et al., 2002; Schneider et al., 2014b), a metabolic syndrome with hyperphagia, late-onset obesity, increased insulin and leptin levels (Toftgaard et al., 2003; Yoshimoto et al., 2006), and an increased severity of EAE, a model of multiple sclerosis (Teuscher et al., 2004, 2007). By comparing EAE-susceptible and -resistant mice strains as well as H₃ receptor KO mice, a functional link between central H₃ receptor signaling and peripheral immune responses was proposed (Krementsov et al., 2013).

With its unique pharmacological properties the H₃ receptor is a major target for development of drugs against various disorders of the brain (Passani et al., 2007; Lin et al., 2011b). H₃ receptor inverse agonists decrease alcohol intake in alcohol-preferring (Lintunen et al., 2001) and normal (Galici et al., 2011) rats and modulate alcohol-induced place preference and locomotor activation in mice (Nuutinen et al., 2010), but not amphetamine-induced place preference (Vanhanen et al., 2015), suggesting new possibilities to treat alcohol dependence.

Early studies on the role of H₃ receptors on gastric acid secretion gave conflicting results as described by Barocelli and Ballabeni (2003). The well recognized role of histamine-producing enterochromaffin-like cells [ECL cells (Hakanson et al., 1986)] in gastric acid secretion and the role of H₂ receptors prompted research using a number of different H₃ receptor ligands and animal models. By using fistula cats and dogs, inhibition of acid secretion with (*R*)- α -methylhistamine (**33**) was found, but these results were not reproduced in some other models (Barocelli and Ballabeni 2003). One confounding factor was the imidazole nature of many studied ligands and their affinity to the H₄ receptor. Recent results with more selective ligands immethridine and methimepip protected the gastric mucosa from HCl-induced damage, and the effect is antagonized by a selective H₃ receptor antagonist A-331440 (Coruzzi et al., 2012). These results suggest that the H₃ receptor-mediated effects are distinct from those mediated by H₄ receptor (Coruzzi et al., 2012).

H₃ receptors have been shown to relax the rabbit middle cerebral artery via an endothelium-dependent mechanism involving both nitric oxide and prostanoid

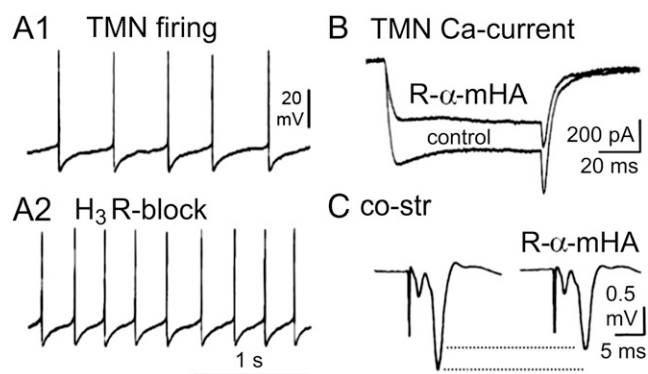


Fig. 12. Electrophysiological actions of H₃ receptor activation in brain slices. (A1) Typical regular firing of a histaminergic tuberomammillary neuron. (A2) Block of the H₃-autoreceptor activation by thioperamide releases the inhibition and thus increases firing rate. (B) Ca²⁺-current in response to depolarization of histaminergic neuron is reduced by the H₃ receptor-agonist *R*- α -methylhistamine (**33**). (C) Glutamatergic corticostriatal synaptic transmission (co-str) is reduced by *R*- α -methylhistamine, an example of an H₃-heteroreceptor action.

release (Ea Kim et al., 1992). Finally, there is a report that H₃ receptor activation can stimulate adrenocorticotrophic hormone release from the pituitary cell line AtT-20 (Clark et al., 1992).

E. H₃-Selective Ligands

A large number of potent ligands for the H₃ receptor have been described, encompassing significant structural diversity. Many of these have been reported as useful pharmacological tools for in vitro or in vivo study and are described here. The number of ligands and structural genera is large, and a number of comprehensive reviews of the structure-activity relationship (SAR) and properties of H₃ receptor ligands have been published (Celanire et al., 2005; Amon et al., 2007; Berlin and Boyce, 2007; Esbenshade et al., 2008; Sander et al., 2008; Gemkow et al., 2009; Tiligada et al., 2009; Lazewska and Kiec-Kononowicz, 2010; Berlin et al., 2011).

1. Agonists. Histamine (1), 2-(1*H*-imidazol-4-yl) ethanamine, is of course the endogenous ligand for histamine receptors, and other imidazole analogs have proven to be useful tools for pharmacological studies (Fig. 13). The methylated analog [³H]*N*^α-methylhistamine (32) (Arrang et al., 1987a) is not selective for H₃ receptors (versus H₁ and H₂ receptors) but because of its high affinity (rat H₃ receptor *K*_d = 2 nM) (Arrang et al., 1983; Hill et al., 1997) and ready availability in tritiated form has found wide use in radioligand competition binding assays. (*R*)- α -Methylhistamine (33) is highly potent (*K*_d = 0.5 nM in rat brain) (Arrang et al., 1985b, 1987b; Hill et al., 1997) and is also used as an in vitro agonist tool. (*R*)- α -Methylhistamine does have significant H₄ receptor activity (binding *pK*_i of 6.85, human H₄ receptor in transfected cells) (Liu et al., 2001a,b; Morse et al., 2001) and *pK*_i = 6.1 at rat H₄ receptor. This agonist also induces water drinking in rodents, a finding used as the basis of an in vivo pharmacological model (Clapham and Kilpatrick, 1993; Ligneau et al., 1998; Fox et al., 2002). Prodrugs of (*R*)- α -methylhistamine have been described with an improved pharmacokinetic profile (Krause et al., 2001; Stark et al., 2001).

Imetit (34) is a readily available potent agonist (rat H₃ receptor *K*_i = 0.1 nM) demonstrating the expected profile of an agonist in vivo, decreasing histamine release ex vivo and turnover (Eriks et al., 1992; Garbarg et al., 1992). More lipophilic ligands have also been described with improved properties. Immepip (35) has high affinity at H₃ receptors but poor selectivity versus H₄ receptors. However, methylation of methimmepip (36) gives an agent with excellent potency (human H₃ receptor *K*_i = 1 nM), agonism (α of 0.9 versus histamine), and selectivity (>2000-fold selectivity over H₁, H₂ receptors and H₄ receptors). Importantly, methimmepip profoundly reduced CNS microdialysate histamine levels at low doses (5 mg/kg i.p.) (Kitbunnadaj et al., 2005). Other lipophilic agonists have also been described in an extensive SAR study (Govoni et al., 2006), and an agonist (37) (human H₃ receptor *K*_i = 0.17 nM, 77% efficacy) was active in vivo in mice in blocking aggression and stress (Ishikawa et al., 2010). Other H₃ receptor agonists have been described with novel structural variations, including immethridine (human H₃ receptor *K*_i = 0.9 nM, 90% agonist efficacy), an analog of immepip wherein the highly basic piperidine moiety is replaced by a less basic pyridinyl moiety (Kitbunnadaj et al., 2004). A particularly interesting ligand is the "protean" (Kenakin, 2002) agonist proxyfan (38) (Gbahou et al., 2003), a compound that does not fit neatly into a rigid categorization of agonist or antagonist, because its properties have been found to depend on the system assessing efficacy, with full agonism, neutral antagonism, and inverse agonism seen. Several other imidazole-containing H₃ receptor ligands have been described, e.g., GT-2331 (39), with some having assay-dependent profiles (Tedford et al., 1999; Liu et al., 2004; Ito et al., 2006).

2. Antagonists. A number of named antagonist ligands have figured prominently in preclinical studies, with clear ability to release neurotransmitters and having efficacy in preclinical animal models. This has motivated continuing research on improved agents with potency, selectivity, and better drug likeness to enable clinical evaluation. Computer modeling strategies

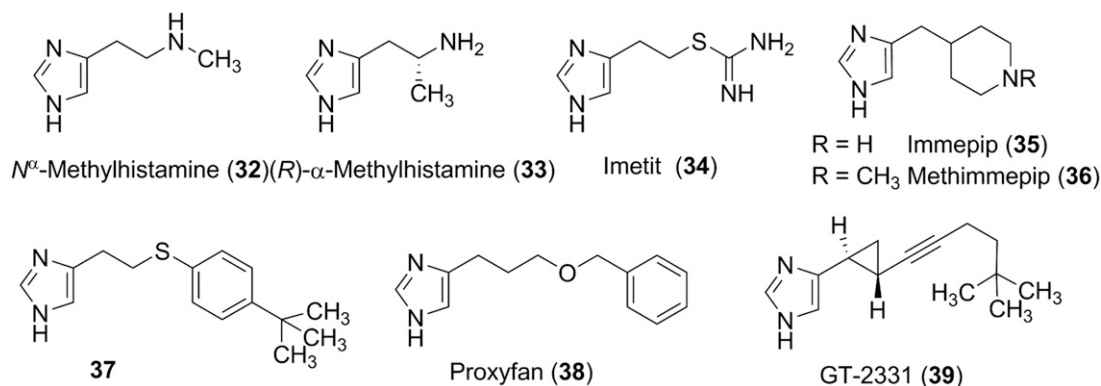


Fig. 13. H₃ receptor agonists.

have been adopted widely in recent years for ligand docking and pharmacophore screening purposes (Schlegel et al., 2007; Levoine et al., 2008) (Fig. 14).

A number of antagonists have advanced to phase I testing and phase II efficacy trials for a number of conditions, including sleep disorders, cognitive disorders in schizophrenia, Alzheimer's disease, attention deficit hyperactivity disorder, and allergic rhinitis.

The first H₃ receptor antagonists were imidazole based, and before the identification of the H₄ receptor, several were widely used "H₃ receptor standards" for preclinical studies, also because of their availability from commercial sources, including thioperamide (**40**), clobenpropit (**41**), and ciproxifan (**42**). Thioperamide is highly potent at rat H₃ receptors with K_i = 4.3 nM (Arrang et al., 1987a; Hill et al., 1997) that has been found broadly effective in vivo in a large number of behavioral models, including elevated plus maze learning, Morris water maze, Barnes maze (Miyazaki et al., 1995; Komater et al., 2005), and others. Clobenpropit (**41**) is likewise highly potent in vitro, with pA₂ = 9.92 in the guinea pig ileum assay (Eriks et al., 1992) and activity in vivo, e.g., in models of working memory, seizure, and Alzheimer's disease (Yokoyama et al., 1994; Zhang et al., 2003; Harada et al., 2004; Huang et al., 2004; Bardgett et al., 2011). Clobenpropit and thioperamide, however, also have potent activity at H₄ receptors (Lim et al., 2009), and thioperamide also is active at 5HT₃ receptors (Leurs et al., 1995b). Ciproxifan is a potent (rat H₃ K_i = 0.5 nM) and selective (Ligneau et al., 1998; Stark et al., 2000) ligand with oral bioavailability, which is effective in a number of preclinical animal models and, thus, has found extensive use as an in vivo reference antagonist, for example, in attentional models, such as electroencephalogram-assessed waking and impulsivity (Komater et al., 2005; Hancock, 2006; Day et al., 2007). SCH-79687 (**43**) is a highly potent (rat H₃ receptor K_i = 1.9 nM) antagonist that reduced congestion in animal models of allergic rhinitis when coadministered with an H₁ receptor antagonist; evidence supports the hypothesis that the efficacy of H₃ receptor antagonists is mediated through peripherally mediated release of norepinephrine from nasal mucosa, because this compound was virtually nonbrain penetrant with a brain/plasma ratio of 0.02 (Varty and Hey, 2002; McLeod et al., 2003).

Nonimidazoles have become the main focus of the H₃ receptor antagonist design work in recent years, because these structures address the class-related issues noted with the early generation of imidazole-based agents, including cytochrome P450 inhibition, relatively poor CNS penetration, and incidence of off-target activity at H₄ receptors or other receptors (Berlin et al., 2011). The first SAR study of potent nonimidazole antagonists disclosed UCL-1972 (**44**), with rat H₃ receptor K_i of 39 nM. In this structure, the imidazole ring was replaced with a tertiary basic amine

(Ganellin et al., 1995). Nonimidazoles as a class have proven much more supportive of combining cross species at rat and human receptors with good drug likeness (CNS penetration, minimal cytochrome P450 inhibition) (Ganellin et al., 1998; Meier et al., 2001). There has been rapid progress in the last decade in finding antagonists with excellent in vivo efficacy in diverse preclinical models, and several prominent compounds have been detailed in the literature. Of particular interest is pitolisant (**45**), also previously known as BF-2.649, BP-2649, or tiprolisant (cf. Meier et al., 2001). This potent (rat K_i = 17 nM, human K_i = 5 nM) antagonist entered clinical trials for a number of indications and has been well characterized preclinically as able to promote wakefulness in animals and humans (Ligneau et al., 2007; Lin et al., 2008; Schwartz, 2011). Antagonists with a second basic amine moiety have been widely described as highly potent, with JNJ-5207852 (**46**) having rat and human K_i of 1.2 and 0.6 nM, and the acetylene analog JNJ-10181457 (**47**) having a rat and human H₃ receptor K_i of 7 and 1.2 nM. These two agents were reported to promote wakefulness in rat, mouse, and dog models (Barbier et al., 2004; Bonaventure et al., 2007), a property of H₃ receptor antagonists as a class (Barbier and Bradbury, 2007). A number of synthetic diamine-containing H₃ receptor antagonists have been described with high in vitro potency. One example of a potent agent is the natural product alkaloid conessine (**48**), with a human H₃ receptor K_i of 5.4 nM, rat H₃ receptor K_i of 25 nM. The core has been elaborated to analogs, whereas the potency and commercial availability of conessine itself suggest potential utility as a tool compound (Coward et al., 2007; Santora et al., 2008; Zhao et al., 2008). The benzofuran ABT-239 (**49**) (human H₃ receptor K_i = 0.45 nM, rat H₃ receptor K_i = 1.35 nM) has been used as a reference antagonist with potent in vivo efficacy in a number of animal models of attention, cognition, schizophrenia, ethanol-associated learning deficit, and Alzheimer's disease (Coward et al., 2005; Fox et al., 2005; Varaschin et al., 2010; Bitner et al., 2011). Heterocyclic benzofuran A-688057 (**50**) was likewise highly brain penetrant, potent in vitro (human H₃ receptor K_i = 0.5 nM, rat H₃ receptor K_i = 3 nM) and effective in animal models in vivo at modest levels of H₃ receptor occupancy (Coward et al., 2007). GSK-189254 (**51**) (human H₃ receptor K_i = 0.1 nM, rat H₃ receptor K_i = 0.7 nM) has been described as broadly effective in a number of animal models, including attentional, memory, pain, and narcolepsy models (Guo et al., 2009; Medhurst et al., 2007; McGaraughty et al., 2012). GSK-189254 (**51**) has also been synthesized in an ¹⁴C-labeled form and used as a PET tracer to empirically measure H₃ receptor occupancy of test compounds in intact animals and in the clinic (Ashworth et al., 2010). GSK-207040 (**52**) (human H₃ K_i = 0.2 nM, rat H₃ K_i = 0.8 nM) and GSK-334329 (**53**) (human H₃ receptor K_i = 0.3 nM, rat H₃ K_i = 0.8 nM) were both found effective in models of neuropathic

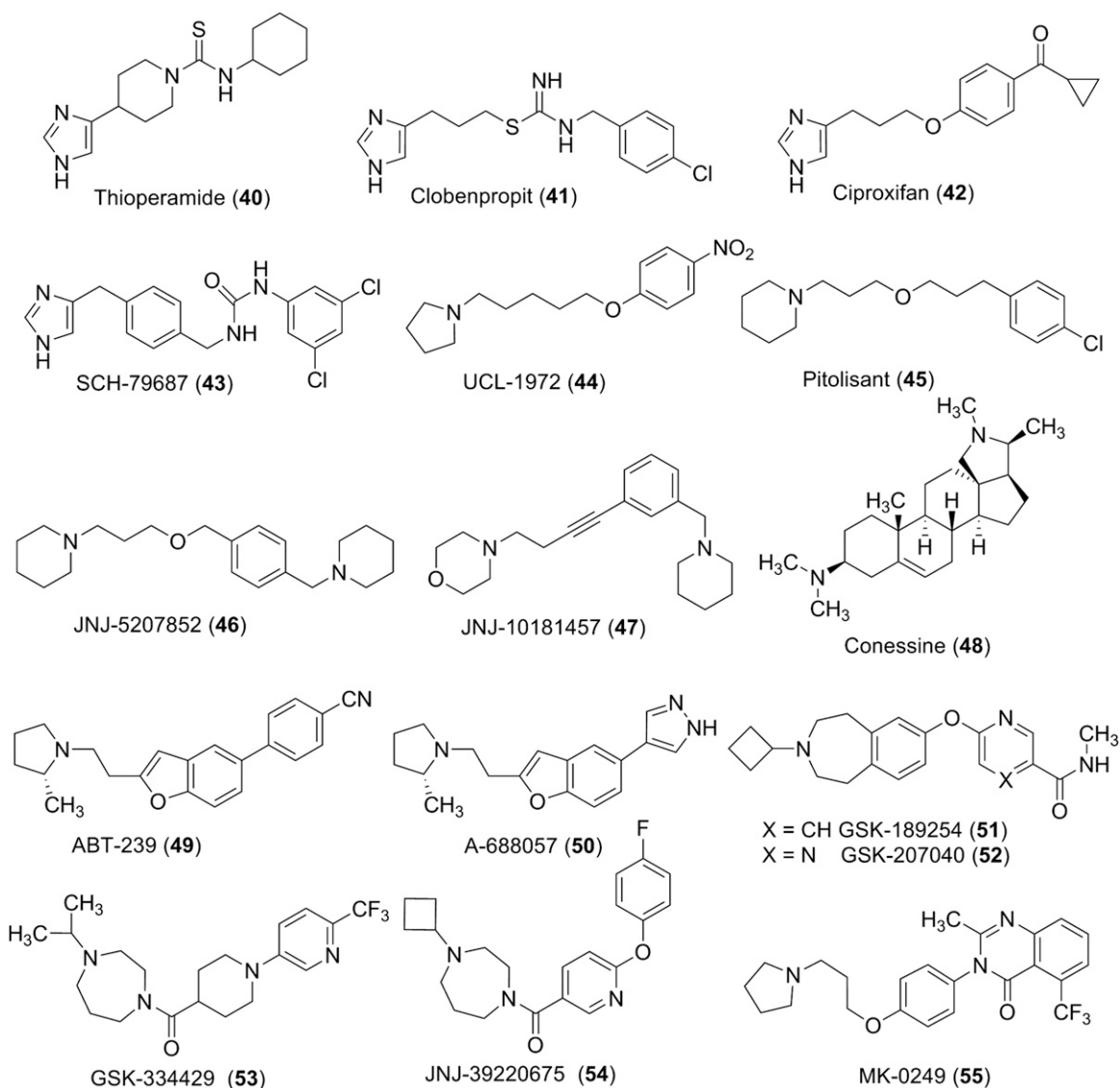


Fig. 14. H₃ receptor antagonists.

pain and capsaicin-induced tactile allodynia and scopolamine-induced memory impairment (Medhurst et al., 2007). A separate report found efficacy in an osteoarthritis pain model for GSK-189254, GSK-334429, and ABT-239 (Hsieh et al., 2010b). Recently, the compound JNJ-39220675 (54) (human H₃ receptor $K_i = 1.4$ nM) was found to reduce ethanol intake in ethanol-preferring rats (Galici et al., 2011) and was found to have decongestant efficacy in an early clinical trial in subjects with allergic rhinitis (Barchuk et al., 2013).

F. Clinical Pharmacology

After a decade of intensive studies (Ligneau et al., 2007; Lin et al., 2008; Schwartz, 2011), a range of H₃ receptor inverse agonists/antagonists have entered advanced clinical development in the last 5 years, with the most advanced being pitolisant (BF2.649, 1-piperidine,

hydrochloride, pitolisant, Wakix, 45) (Dauvilliers et al., 2013) having been officially filed for licensing by Bioprojet early in 2014 for use in refractory narcolepsy. This is the completion of an impressive research story spanning 40 years, initiated back in the mid-1970s, when histamine was first described as a neurotransmitter, and the pharmacological and molecular identification of the H₃ receptor in the mid-1980s and late-1990s, respectively. Narcolepsy is characterized by excessive diurnal sleepiness and can occur alone or as part of other neurologic disorders (e.g., Parkinson's disease). On the basis of the wake-inducing properties of H₃ receptor blockade, pitolisant (45) was developed, together with an apparent ideal pharmacokinetic profile, where a once-a-day dose maintains attention over the day, but, importantly, allows individuals to sleep at night (Iannone et al., 2010; James et al., 2011; Schwartz, 2011). Preclinical studies have also suggested the lack of drug abuse liability

for pitolisant in rodent and primate models, in contrast to modafinil (Uguen et al., 2013). In a double-blind, randomized, parallel-group controlled trial performed with 95 cases recruited across Europe in 32 sleep centers, pitolisant at doses up to 40 mg was efficacious on excessive daytime sleepiness compared with placebo. Over the 8-week treatment period, mean Epworth Sleepiness Scale score reductions were -3.4 in the placebo group, -5.8 in the pitolisant group, and -6.9 in the modafinil group. Pitolisant was well tolerated (with only one patient displaying a serious side effect, namely abdominal discomfort) compared with the previous gold standard, modafinil, where multiple issues arose (Dauvilliers et al., 2013). A recent retrospective study determined the benefits of pitolisant in patients with idiopathic hypersomnia and narcolepsy refractory to stimulants, including modafinil. Twenty-three to thirty-eight percent of the 78 patients receiving pitolisant (daily 5- to 50-mg dose) displayed a positive benefit/risk ratio (Leu-Semenescu et al., 2014).

A more modest study with an H_3 receptor inverse agonist, MK-0249 (**55**) did not significantly affect maintenance of wakefulness test battery. However, the pattern of improvement on a range of subjective ratings and psychomotor performance end points suggested that MK-0249 (**55**) improved some aspects of cognition and performance not captured by the maintenance of wakefulness test (Herring et al., 2013). A number of other compounds developed by major players in this field have been investigated, with multiple trials listed in www.clinicaltrials.gov to date but yet to be reported. These include a series of phase I PET occupancy trials with PF-03654746, AZD5213, and GSK239512 distribution investigation after oral administration. H_3 heteroreceptors modulate acetylcholine levels in cortical regions of the brain, a fact that suggests potential for H_3 receptor blockade in reversing scopolamine-induced cognitive deficits. This was investigated in small acute clinical study, where 28 individuals completed a double-blind, placebo-controlled, five-period crossover study, and cognitive function was assessed using the Groton Maze Learning Task as the primary outcome measure. Interestingly, although these primary end points were not met at the extended time point (up to 12 hours), administration of either MK-3134 or donepezil improved performance at the 2-hour time point compared with scopolamine alone. Moreover, it appeared that the combination of MK-3134 and donepezil suppressed the scopolamine negative effect to a greater extent than either drug alone (Cho et al., 2011). Further clinical trials have been completed, focused on evaluation of the efficacy and safety of GSK239512 in Alzheimer's disease, using a randomized, double-blind, placebo-controlled study and cognitive impairment in schizophrenia. The initial report showed that GSK239512 displayed appropriate tolerability up to a maximum dose of $80 \mu\text{g}/\text{day}$ in patients with Alzheimer's disease, with some preliminary

evidence for positive effects on attention and memory with modest effect sizes (Nathan et al., 2013). A larger follow study (over 190 mild/moderate Alzheimer's cases) reported GSK239512, up-titrated over 4 weeks ($10\text{--}20\text{--}40\text{--}80 \mu\text{g}$) followed by a 12-week maintenance phase, compared with sham controls, although it did not display improvement in working memory and other cognitive outcomes, however, it exhibited improved episodic memory, with a reasonable safety profile (Grove et al., 2014). Further large trials are required to investigate this differential responsiveness. A number of reports studying H_3 receptor inverse agonists have indicated potential in vivo for anticonvulsive activity utilizing various models, including the maximal electroshock-induced and pentylenetetrazole-kindled seizure models in rodents (Sadek et al., 2014a,b).

In a randomized multicenter, double-blind, placebo- and active-controlled, parallel group study on adult attention-deficit hyperactivity syndrome on bavisant (JNJ-31001074), the drug did not differ from placebo, whereas atomoxetine hydrochloride and osmotic release oral system methylphenidate were effective (Weisler et al., 2012). A clinical trial with the same drug was also listed at clinicaltrials.gov but the trial has not been initiated. Thus, this indication for which there is experimental support from rodent studies and several drug candidates tested for safety and side effects in humans has not been tested. In a randomized crossover study the H_3 receptor inverse agonist MK-0249 was not superior to placebo for the treatment of cognitive impairment in patients with schizophrenia (Egan et al., 2013). In conclusion, the expectations for extensive clinical use of H_3 receptor inverse agonists have yet to be realized.

Peripheral indications have also been explored. In combination with fexofenadine, single doses of PF-03654746 produced a reduction in allergen-induced nasal symptoms in a small 20 patient trial using an acute nasal allergen challenge with a bolus of ragweed (Stokes et al., 2012).

V. Histamine H_4 Receptor

The H_4 receptor is the most recently discovered histamine receptor. The cloning of the H_3 receptor provided a template for the search of other histamine receptors. This culminated with six independent groups reporting the cloning of the H_4 receptor (Nakamura et al., 2000; Oda et al., 2000; Liu et al., 2001a; Morse et al., 2001; Nguyen et al., 2001; Zhu et al., 2001; O'Reilly et al., 2002). Since that time much research has focused on characterizing the receptor's role in inflammatory process, because it originally appeared to be predominantly expressed in hematopoietic cells.

A. Receptor Structure

The H_4 receptor displays similarities to the H_3 receptor in terms of gene and protein secondary structure (Coge et al., 2001a,b). The human H_4

receptor gene is present as a single copy per haploid genome on chromosome 18q11.2, spans more than 21 kbp, and contains three exons together with two large introns (7867 and >17,500 bp). The coding regions encode amino acids 1–65, 66–119, and 120–390, respectively. The transcript size of the gene is approximately 3.7 or 4.5 kb, which is explained by at least two polyadenylation sites 0.8 kb apart (Coge et al., 2001b). The open reading frame (1172 bp) encodes a 390-amino-acid polypeptide that forms the classic 7-transmembrane structure of the family A rhodopsin-like GPCR. A series of polymorphisms have been identified and confirmed by SNP analysis involving Caucasian, Chinese, Japanese, African-American, and Sub-Saharan African individuals, including V138A and R206H. The occurrence of A138 or H206 is 10-fold higher than the V138 or R206 version, respectively. Further SNPs have been found in intron 1, 33 in intron 2, and 13 in the 3'-untranslated region, as well as a frame-shift at the C terminus of the protein (<http://www.ncbi.nlm.nih.gov/SNP>).

It is possible that the H₄ receptor can exist in dimeric or oligomeric forms. Based on immunoblotting techniques, various structural forms of the H₄ receptor have been reported: 44 kDa (unglycosylated monomer), 46 kDa (glycosylated monomer), 85 kDa (glycosylated dimer), and >250 kDa (oligomeric structures) (Nguyen et al., 2001; van Rijn et al., 2006). Based on biochemical (immobilized metal affinity chromatography) and biophysical techniques (time-resolved fluorescence resonance transfer and BRET) in transfected cells, the human H₄ receptor can exist as dimeric or oligomeric species (van Rijn et al., 2006). However given the uncertainties around the selectivity of H₄ receptor antibodies (see section V.C) and lack of direct evidence in primary cells, it is still uncertain as to whether oligomerization occurs in native tissues and cells or whether it has physiologic consequences.

In addition to this, two human H₄ receptor isoforms have been identified and designated H₄ receptor 302 and H₄ receptor 67, the former lacking residues 68–155, whereas the latter is prematurely terminated at residue 67. These isoforms are the result of alternative splicing, but do not bind histamine or inverse agonists. In heterologous expression systems, these isoforms have been shown to elicit dominant negative effects on the full-length isoform by decreasing the B_{\max} of [³H]histamine binding sites as well as retaining the full-length receptor intracellularly via oligomerization (van Rijn et al., 2008).

A study in human peripheral blood leukocytes showed an upregulation of the truncated isoform of the H₄ receptor (H₄R), but not the full-length H₄ receptor during grass pollen season, suggesting a possible regulatory effect on H₄ receptor signaling (Hodge et al., 2013). Whether these different isoforms are expressed in primary cells at the protein level and whether they are

physiologically relevant is currently unknown. Moreover, whether there are also functional H₄ receptor isoforms, as observed for the H₃ receptor, is currently unknown. Yet the similar intron/exon structure might give rise to functional H₄ receptor isoforms.

The identification of the human H₄ receptor gene prompted the cloning of the rat, mouse, canine, guinea pig, and porcine H₄ receptor orthologs (Oda et al., 2000; Liu et al., 2001b; Jiang et al., 2008). These are modestly homologous to the human ortholog, with sequence homology ranging from 67 and 72%. The monkey H₄ receptor was subsequently cloned in 2005 and displays a high homology of 92% (Oda et al., 2005). Partial sequences of other species orthologs have been identified but not published. Species differences in pharmacology (ligand binding and signaling efficacy) are profound, also depending on readout systems (Nordemann et al., 2013), and several molecular features for the observed species differences have been elucidated (Liu et al., 2001b; Lim et al., 2008, 2010; Schnell et al., 2011). Whereas proximal readout systems such as [³²P]GTPase or [³⁵S]GTPS binding assays show pronounced differences between species orthologs, more distal reporter gene assays revealed less pronounced differences. Species splice isoforms have yet to be reported.

The H₄ receptor possesses the prototypical acidic residue (Asp94^{3.32}) in TM3, which interacts with the amine group of histamine (**1**; Fig. 3). In addition to the conserved aspartate, a glutamate residue is also present in TM5 (Glu 182^{5.46}), consistent with the H₃ receptor, and is another key histamine binding residue (Shin et al., 2002; Uveges et al., 2002). As discussed previously for the H₃ receptor, the interaction of the imidazole ring with this glutamate residue is most likely responsible for the relatively high affinity of the H₄ receptor for histamine. This amino acid is also important in binding smaller agonist ligands (e.g., VUF8430) (Lim et al., 2008). The H₄ receptor also possesses cysteine residues that potentially form disulfide bridges spanning TM3 and ECL2. Interestingly, using a chimeric and site-directed mutagenesis approach it was shown that the ECL2 loop is also involved in the binding pocket. Phe169 in ECL2 was identified as the single amino acid responsible for the differences in histamine affinity between the human and rodent H₄ receptor (Lim et al., 2008). Final confirmation of this suggestion awaits successful crystallization.

Interestingly, the H₄ receptor does not contain the so-called “ionic lock” between the highly conserved R^{3.50} of the DRY motif at the end of TM3 and a negative charged D/E^{6.30} in TM6, which in many GPCRs is considered to hold the receptor in an inactive state (Smit et al., 2007). Yet, the H₄ receptor contains an alanine residue at position 6.30, and mutation of this residue (e.g., into glutamate) does not really alter the constitutive signaling (Schneider et al., 2010a). A

pseudoionic lock has been claimed for differentiating (partial) agonist from antagonist binding modes (Werner et al., 2010).

B. Signal Transduction Mechanisms

A detailed understanding of signal transduction mechanisms downstream of H₄ receptor activation is emerging. Like the structurally related H₃ receptor, the H₄ receptor belongs to the class of G_i/G_o-coupled GPCRs. The primary second messenger appears to be increased intracellular Ca²⁺ (Raible et al., 1994; Buckland et al., 2003; Hofstra et al., 2003; Dijkstra et al., 2007; Jemima et al., 2014), although activation of kinases has also been reported (Gutzmer et al., 2005, 2009; Desai and Thurmond, 2011; Ferreira et al., 2012; Mommert et al., 2012; Karlstedt et al., 2013). The best studied native cell type that expresses the H₄ receptor is the human eosinophil. The H₄ receptor-mediated activity in these cells such as cell shape change, Ca²⁺ mobilization, and actin polymerization is sensitive to inhibition by the G_iα/G_oα-ADP-ribosylating toxin pertussis toxin (Raible et al., 1994). Along the same lines, H₄ receptor-mediated Ca²⁺ mobilization in mouse bone marrow-derived mast cells is also pertussis toxin sensitive (Hofstra et al., 2003). The pertussis toxin data suggest that the H₄ receptor couples to G_iα- or G_oα-subunits; however, because myeloid cells express G_iα-subunits (predominantly G_iα2 and, to a lesser extent, G_iα3, but not G_iα1) and do not express G_oα-subunits (Birnbauer, 2007), it is very likely that G_iα2- and G_iα3 G protein α-subunits represent the cognate coupling partners of the H₄ receptor in these native cells (Fig. 4).

Transfected cell systems also support the conclusion that the H₄ receptor is a G_i-coupled GPCR. Expression of the H₄ receptor in SK-N-MC neuroblastoma cells leads to ligand-dependent inhibition of forskolin-stimulated cAMP accumulation (Nakamura et al., 2000; Oda et al., 2000; Liu et al., 2001a; Lim et al., 2005). The inhibitory effect of the H₄ receptor on cAMP accumulation is pertussis toxin sensitive, indicative for G_i protein coupling (Oda et al., 2000).

In further support of coupling of the H₄ receptor to G_iα proteins, to detect H₄ receptor-mediated Ca²⁺ mobilization in a commonly used mammalian expression system such as HEK293 cells, the H₄ receptor has to be cotransfected with the “universal” G protein G15α or G16α (Oda et al., 2000) or a chimeric G_qα protein in which the last five C-terminal amino acids are replaced by those of G_iα/G_oα-subunits (Coward et al., 1999; Liu et al., 2001a; Morse et al., 2001; Zhu et al., 2001; Jiang et al., 2008).

G protein coupling of the H₄ receptor was further analyzed in the Sf9 insect cell expression system. One concern of this system is that the receptor expressed in Sf9 insect cells may differ from the H₄ receptor expressed in mammalian cells. However, overall, it appears that the H₄ receptor expressed in Sf9 insect cells and mammalian cells are similar (Schneider et al.,

2009). The human H₄ receptor couples only poorly, if at all, to insect cell G proteins as assessed by GTPγS binding and GTPase activity (Schneider et al., 2010b). Nonetheless, even in the absence of mammalian G proteins, the human H₄ receptor exists in a state that exhibits high agonist affinity. Evidently, because G proteins are not required for this state, high-affinity [³H]histamine binding is GTPγS insensitive. These properties of the human H₄ receptor are in marked contrast to several other G_i-coupled receptors, including the formyl peptide receptor that, like the H₄ receptor, is expressed in myeloid cells (Ye et al., 2009). Moreover, GTPγS-insensitive [³H]histamine binding to the H₄ receptor has also been observed for the H₄ receptor expressed in mammalian cells (Lim et al., 2010). The lack of interaction with endogenous insect G proteins makes this an excellent system for exploring the interaction with mammalian G proteins. When reconstituted with various G protein α-subunits and the Gα₁α₂-complex, human H₄ receptor exhibits clear preference for G_iα₂ (Schneider et al., 2009, 2010a), which is consistent with the fact that this is the most likely partner in eosinophils and mast cells. There is some coupling to Gα₁ and G_iα₃, suggesting that these subunits may also be important in some cell types. However, the coupling to G_oα, a G protein α-subunit predominantly expressed in neuronal and neuroendocrine cells (Birnbauer, 2007), is poor (Schneider et al., 2009).

The human H₄ receptor coupled to G_iα₂ exhibits high constitutive activity as is evident by high basal GTPγS binding and GTPase activity, relatively small agonist effects on guanine nucleotide exchange, and profound inhibitory effects of the inverse agonist thioperamide (Schneider et al., 2009). Amino acids F169 and S179 appear to play key roles for this high constitutive activity of the human H₄ receptor (Wifling et al., 2015). Because the human H₄ receptor exhibits high constitutive activity (Lim et al., 2005; Schneider et al., 2010b), H₄ receptor agonists decrease cAMP accumulation, whereas H₄ receptor inverse agonists increase cAMP accumulation (Lim et al., 2005; Kottke et al., 2011). In marked contrast to the situation with recombinant systems, there is little, if any, evidence as yet for constitutive activity of the H₄ receptor in native systems.

In primary cells, it appears that the H₄ receptor mediates signaling via increases in calcium (Raible et al., 1994; Buckland et al., 2003; Hofstra et al., 2003; Dijkstra et al., 2007; Jemima et al., 2014). In addition kinases such as ERK, phosphoinositide 3-kinase (PI3K), and p38 and the transcription factor activating protein-1 have been shown to be activated by the H₄ receptor (Gutzmer et al., 2005, 2009; Desai and Thurmond, 2011; Ferreira et al., 2012; Mommert et al., 2012; Karlstedt et al., 2013).

The different H₄ receptor species orthologs exhibit different pharmacological properties, perhaps related to a relatively low level of homology (Liu et al., 2001b;

Jiang et al., 2008). For example, the affinity of histamine and various other ligands vary between the species. In addition, studies measuring inhibition of cAMP-dependent reporter gene expression and chimeric G protein-mediated increases in cytosolic calcium ion concentration or reporter gene expression indicated that not only the human H₄ receptor, but also canine, murine, rat, and guinea pig H₄ receptors couple to G_i proteins (Liu et al., 2001b; Jiang et al., 2008). In Sf9 cells, human, canine, rat, and murine H₄ receptor all couple to G_i proteins as assessed by agonist-stimulated GTP hydrolysis (Schnell et al., 2011). These studies confirmed the previously observed pharmacological differences between H₄ receptor species orthologs and also revealed substantial differences in constitutive activity of the four species orthologs. Specifically, only human H₄ receptors, but not canine and murine H₄ receptors, possess high constitutive activity as assessed by inhibitory effects of thioperamide on basal GTP hydrolysis (Schnell et al., 2011).

C. Anatomic Framework

Identification of the expression pattern of the H₄ receptor has been hampered by several issues. mRNA levels can be used to determine if the H₄ receptor message is expressed in a cell type or tissue; however, it does not provide evidence that the protein is expressed. Furthermore, it can be difficult to determine exactly which cell types express the RNA in tissues, and the purity level of primary cells can lead to false positive signals. Finally, the expression of RNA may depend on the environment, because it is known that message levels and activity change in response to inflammatory stimuli and to the state of the cell. For example, the H₄ receptor was undetectable on human CD8⁺ T cells in one report (Ling et al., 2004), whereas another (Gantner et al., 2002) showed a function for the receptor in these cells by pharmacological means and mRNA expression; however, the level of expression varied from donor to donor. A major issue is the lack of a widely accepted and available antibody specific for the receptor. In particular the selectivity of the available antibodies has been questioned and care should be taken with interpreting expression data based on these antibodies. Specifically, one study (Beermann et al., 2012b), using stringent controls, showed that three commercially available antibodies directed against the human and mouse H₄ receptor do not specifically recognize the H₄ receptor in various receptor formats, including fluorescence-activated cell sorting and immunoblotting. This study included controls with epitope-tagged H₄ receptors and H₄ receptor knockout cells and is in line with a series of previous studies on various biogenic amine GPCRs indicating that many GPCR antibodies distributed commercially do not fulfill the criteria necessary for receptor expression studies (Michel et al., 2009). A general caveat for H₄ receptor work, or any other field for that matter, is that

one cannot rely solely on mRNA data, antibody data, or pharmacology data with a single ligand to prove the existence of the receptor. The best approach currently is to use a combination of techniques with the definitive answer being given by pharmacological activities defined by multiple ligands.

One of the best examples of using pharmacology to define the receptor function comes from the early work with eosinophils. In the late 1970s it was noted that histamine could induce eosinophil chemotaxis via non-H₁ receptor, non-H₂ receptor (Clark et al., 1975, 1977; Wadee et al., 1980). Later it was discovered that histamine-stimulated increases in intracellular Ca²⁺ in eosinophils were blocked by thioperamide, impromidine, and burimamide, but not by pyrilamine or cimetidine, suggesting at the time that the effects of histamine were H₃ receptor mediated (Raible et al., 1994). However, other data did not match the known pharmacology of the H₃ receptor, including the fact that (*R*)- α -methylhistamine was over an order of magnitude less potent than histamine. The cloning of the H₄ receptor and its pharmacological characterization indicated that this pharmacology matched that of the new receptor and it was subsequently shown that indeed the H₄ receptor mediates Ca²⁺ responses and chemotaxis of eosinophils (Buckland et al., 2003; Ling et al., 2004).

At the mRNA level, the H₄ receptor appears to be most strongly expressed in bone marrow, but expression can also be detected in peripheral blood, spleen, thymus, as well as in lung, small intestine, colon, and heart (Nakamura et al., 2000; Oda et al., 2000; Liu et al., 2001a; Morse et al., 2001; Nguyen et al., 2001; Zhu et al., 2001). Some have also indicated H₄ receptor expression in liver, brain, skeletal muscle, gastrointestinal tract, and epidermal tissue (Nakamura et al., 2000; Coge et al., 2001b; O'Reilly et al., 2002; Buckland et al., 2003; Sander et al., 2006; Rossbach et al., 2009, 2011; Yamaura et al., 2009). However, these organs also contain, to different extents, hematopoietic cells that may account for the mRNA signals. H₄ receptor expression has been detected in synovial cells from rheumatoid arthritis and osteoarthritis patients and localized to both fibroblast-like and macrophage-like cells from rheumatoid arthritis synovial tissue, but this expression has not been confirmed by any functional data (Ikawa et al., 2005; Ohki et al., 2007; Grzybowska-Kowalczyk et al., 2008). The exact details of the expression of the receptor are still emerging and are complicated by the fact that the receptor levels and activity change in response to inflammatory stimuli and to the state of the cell. Furthermore, there is evidence that the receptor can be upregulated by inflammatory stimuli. For example, it was shown that the receptor expression on monocytes could be upregulated by interferon (IFN) γ treatment and that interleukin (IL)-4 upregulated the receptor expression on T cells (Dijkstra et al., 2007; Gutzmer et al., 2009). In addition it has been shown that the receptor is upregulated in all peripheral

organs 24 hours after inducing sepsis in a mouse model and in the kidney of diabetic rats (Matsuda et al., 2010; Rosa et al., 2013).

Expression coupled with function defined by pharmacological methods has been shown on mast cells; eosinophils; neutrophils; dendritic cells; Langerhans cells; natural killer cells; monocytes; T cells, including $\gamma\delta$ T cells, T helper 1, 2, and 17 cells; keratinocytes; inflammatory dendritic epidermal cells; and fibroblasts (Gantner et al., 2002; Hofstra et al., 2003; Ling et al., 2004; Lippert et al., 2004; Gutzmer et al., 2005, 2009; Sander et al., 2006; Damaj et al., 2007; Dijkstra et al., 2007, 2008; Godot et al., 2007; Bäumer et al., 2008; Ikawa et al., 2008; Yamaura et al., 2009; Gschwandtner et al., 2010, 2011, 2012, 2013; Truta-Feles et al., 2010; Mommert et al., 2012; Glatzer et al., 2013; Mirzahosseini et al., 2013; Cowden et al., 2014; Czerner et al., 2014; Dib et al., 2014; Jemima et al., 2014). In addition, expression data, but as to date no functional data, have been reported in epithelial cells and basophils (Hofstra et al., 2003; Sander et al., 2006). However, care must be taken in interpreting all of these data even where expression appears to correlate with pharmacological activity. For example, some groups report mRNA in monocytes and CD8⁺ T cells whereas others do not, which may be attributed to intrasubject variability in expression or in different cell isolation and detection methods used (Gantner et al., 2002; Ling et al., 2004; Dijkstra et al., 2007; Werner et al., 2014). In addition, although most of the pharmacological data are compelling, some details require further scrutiny. For example, potency of thioperamide reported by Damaj et al. (2007) for natural killer cells and monocyte-derived dendritic cells is higher than that expected from binding data in recombinant systems (Liu et al., 2001a). A similar observation can be noted in the inhibition of CCL2 secretion in human monocytes, where the potency of clobenpropit is much higher than histamine in contrast to the affinity data in recombinant systems (Liu et al., 2001a; Dijkstra et al., 2007). These issues are clearly highlighted in the work of Gschwandtner et al. (2013) where six different H₄ receptor agonists were shown to inhibit IL12p70 production in human monocytes, but in most cases this was only partially blocked by an H₄ receptor antagonist. The situation is not as clear-cut as it first seems and warrants further investigation.

Recent studies provided evidence that genetic variations of the H₄ receptor are associated with inflammatory diseases. Certain polymorphisms of the human H₄ receptor gene that should result in an increased expression or signaling of the receptor were associated with atopic dermatitis (Yu et al., 2010b). Along this line, keratinocytes derived from patients with atopic dermatitis expressed higher levels of the H₄ receptor mRNA compared with keratinocytes from patients without skin disease or psoriasis (Glatzer et al., 2013). In asthma, there

appeared to be a link between three single nucleotide polymorphisms in the H₄ receptor gene and infection-induced asthma (Simon et al., 2012). mRNA encoding the H₄ receptor was significantly higher expressed and H₄ receptor gene copy numbers were significantly amplified in patients with systemic lupus erythematosus compared with healthy controls. Moreover, H₄ receptor gene copy numbers correlated to the incidence of arthritis, proteinuria, and antinuclear antibody abnormalities in systemic lupus erythematosus (Yu et al., 2010a).

There is some evidence that the H₄ receptor may be expressed in the nervous system, but this remains controversial and needs further research. In general, results obtained with antibodies have not always been verified with parallel analyses of mRNA expression, and there is currently no consensus about expression of H₄ receptor in various parts of the nervous system. In the human brain, expression of H₄ receptor mRNA has been reported in the amygdala, cerebellum, corpus callosum, cortex frontal cortex, hippocampus, and thalamus in samples of a commercial mRNA panel (Strakhova et al., 2009b). Immunohistochemistry suggested that lamina I–VI of the murine and human cerebral cortex may express the H₄ receptor with the strongest expression in layers IV and VI for the latter (Connelly et al., 2009). Expression has also been reported in the murine hippocampus, granule cell layer of the cerebellum, the thalamus, and in the spinal cord (Connelly et al., 2009; Strakhova et al., 2009b). The expression pattern in mouse and rat brains appeared to be similar to that in humans. However, quantitative reverse-transcription polymerase chain reaction and *in situ* hybridization data from many mammalian CNS areas are still not available to support the findings. In the rat, expression of the H₄ receptor by immunohistochemistry was detected in approximately one-third of dorsal root ganglion neurons of all size classes. Immunoreactivity was also present in laminae I, II, and IV in spinal cord, in a pattern consistent with expression on primary afferent terminals (Strakhova et al., 2009b).

mRNA expression of both the full-length H₄ receptor and one of the deletion forms has also been detected in a rat brain endothelial cell line using reverse-transcription polymerase chain reaction and sequencing (Karlstedt et al., 2013). The H₄ receptor may also be involved in the vestibular system, because expression of the receptor has been reported in vestibular nucleus neurons and ganglia in rats (Desmadryl et al., 2012; Zhang et al., 2013). Overall, the presence of the H₄ receptor in afferent pathways including dorsal root ganglion, spinal cord dorsal horn, and thalamus, as well as in other CNS areas, appears to be entirely consistent with a role in sensory signaling. The identity of the H₄R-expressing sensory neurons in humans is yet to be established, but expression on skin innervating

sensory neurons was shown in mice (Rossbach et al., 2011).

D. Function

One of the first functions ascribed to the H₄ receptor was in mediating chemotaxis. Histamine acting via the H₄ receptor has been shown to induce chemotaxis of a number of different cell types. In mast cells, histamine was shown to induce chemotaxis, and these effects were abrogated by treatment with H₄ receptor antagonists but not antagonists to the other histamine receptors (Hofstra et al., 2003; Thurmond et al., 2004). Furthermore, neither response was seen in mast cells from H₄R-deficient mice. Histamine also enhanced mast cell precursor chemotaxis to CXCL12 via a priming effect, but not to stem cell factor or leukotriene B₄ (Godot et al., 2007). This enhanced chemotaxis was blocked by H₄ receptor antagonists, but not antagonists for the H₁ receptor or H₂ receptor. In eosinophils, histamine or H₄ receptor agonists induced chemotaxis, cell shape change, actin polymerization, and synergized with other chemotactic agents (O'Reilly et al., 2002; Buckland et al., 2003; Ling et al., 2004; Lim et al., 2005; Yu et al., 2010c). Furthermore, histamine activation of the H₄ receptor induced adhesion molecule upregulation in eosinophils (Buckland et al., 2003; Ling et al., 2004). However, compared with eotaxin and formyl peptides, the stimulatory effects of histamine on eosinophil chemotaxis are small (Reher et al., 2012). Moreover, in contrast to the formyl peptide receptor, the H₄ receptor does not mediate reactive oxygen species formation or eosinophil peroxidase release (Reher et al., 2012). Dendritic cells migration can also be modulated by the H₄ receptor (Gutzmer et al., 2005; Damaj et al., 2007; Bäumer et al., 2008; Gschwandtner et al., 2010). Histamine-induced migration of dendritic cells in vitro or ex vivo and a H₄R-dependent migration of dendritic cells was detected in vivo in mice during an allergic response (Cowden et al., 2010b). The migration of Langerhans cells has also been shown to be mediated by the H₄ receptor (Gschwandtner et al., 2010). An ex vivo assay was used to show that the H₄ receptor could mediate chemotaxis of Langerhans cells from epidermis from healthy donors or patients with bullous pemphigoid (Gschwandtner et al., 2010). In mice, injection of an H₄ receptor agonist induced the migration of Langerhans cells in vivo (Gschwandtner et al., 2010). Chemotaxis of monocytes, $\gamma\delta$ T cells, and fibroblasts has also been shown to be mediated via the H₄ receptor (Damaj et al., 2007; Kohyama et al., 2010; Truta-Feles et al., 2010), although it was criticized (in particular for monocytes) that these data have only been published in single studies and have not been confirmed by other groups (Werner et al., 2014).

Migration of cells in response to H₄ receptor stimulation has also been demonstrated in animal models or inflammation. The role of H₁ receptor and H₄

receptor in an ovalbumin specific murine dermatitis model was investigated with the adoptive transfer of ovalbumin-specific Th2-cells (Mahapatra et al., 2014). Treatment of recipient mice with either H₁ receptor or H₄ receptor antagonists resulted in a reduced migration of Th2 cells to sites of allergen challenge. Cytokine production in skin draining lymph nodes was only reduced by combined application of H₁ receptor and H₄ receptor antagonist, whereas mast cell counts were not altered by either H₁ receptor, H₄ receptor, or combined blockade. The paper does not state any results with regard to the effect of H₁ receptor or H₄ receptor blockade on skin inflammation.

Another study investigated carrageenan-induced pleurisy in mice (Ahmad et al., 2014). The administration of JNJ-7777120 (**58**) 1 hour before carrageenan application decreased both the number of T-cell subsets and G_{ITR}(+), G_{ITR}(+) IL-17A(+)-expressing T cells, and the production of Th1/Th17 cytokines, whereas the administration of 4-methylhistamine (**17**) increased both the numbers of CD4(+), CD25(+), CD4(+) CD25(+), G_{ITR}(+), G_{ITR}(+) IL-17A(+)-expressing T cells and the levels of T helper type 1 (Th1)/Th17 cytokines. JNJ-7777120 had anti-inflammatory effects, whereas 4-methylhistamine worsened inflammation in this model.

In addition to chemotaxis, the H₄ receptor is also involved in cytokine release from a number of cell types. It has been shown that histamine can induce IL-16 production from CD8⁺ T cells (Gantner et al., 2002). This can be blocked by H₂ receptor or H₄ receptor antagonists but not by antagonists of the H₁ receptor. The H₄ receptor inhibited IL-12p70 release from human monocyte-derived dendritic cells and inflammatory dendritic epidermal cells (Gutzmer et al., 2005; Dijkstra et al., 2008). In mouse dendritic cells, Toll-like receptor (TLR)-stimulated production of IL-6, KC, MIP-1 α , interferon- γ -induced protein 10 (IP-10), and tumor necrosis factor α (TNF α) was blocked by an H₄ receptor antagonist and was attenuated in dendritic cells from H₄R-deficient mice; however, in this case, IL-10 and IL-12p70 were unchanged (Dunford et al., 2006). Regulation of cytokine production from dendritic cells appears to impact their ability to polarize CD4⁺ T cells to a Th2 phenotype, and histamine acting via the H₄ receptor may also mediate cross-presentation to CD8⁺ T cells (Dunford et al., 2006; Amaral et al., 2007). Histamine downregulated the production of CCL2 in human monocytes, Langerhans cells, inflammatory dendritic epidermal cells, and slan-dendritic cells (Dijkstra et al., 2007, 2008; Gschwandtner et al., 2011, 2012). Furthermore, other Th1-promoting cytokines and chemokines were downregulated in a variety of human antigen-presenting cells via H₄ receptor stimulation, such as downregulation of TNF α , interferon α , and CXCL8 on plasmacytoid dendritic cells (Gschwandtner et al., 2011, 2012), and IP-10 on monocytes and myeloid dendritic cells (Glatzer et al., 2014). Stimulation of the H₄ receptor

induced IL-31 production in peripheral blood mononuclear cells (PBMC) or Th2 polarized T cells, and this production was significantly increased in PBMC from subjects with atopic dermatitis compared with healthy controls (Gutzmer et al., 2009). The receptor also mediated IL-4 and IFN γ production from murine natural killer T cells in vivo (Leite-de-Moraes et al., 2009). Cytokine and chemokine production in vivo has also been shown to be regulated by the H₄ receptor in several disease models. Reduction in Th2 cytokines such as IL-4, IL-5, and IL-13 levels were observed after H₄ receptor antagonist treatment in mouse models of asthma, allergic rhinitis, and allergic contact dermatitis (Takahashi et al., 2009; Cowden et al., 2010a; Seike et al., 2010). H₄ receptor antagonist treatment reduced tissue TNF α levels in a rat colitis model, and several inflammatory cytokines and chemokines were reduced in a model of Th2-dependent dermal inflammation (Varga et al., 2005; Cowden et al., 2010a). IFN γ synthesis of murine T helper cells was also reduced by the H₄ receptor antagonist (Vauth et al., 2012). The levels of lipid mediators are also affected by the H₄ receptor, with antagonists showing reduction in leukotriene B₄ and prostaglandin D₂ in models of pleurisy and peritonitis, respectively (Takeshita et al., 2003; Strakhova et al., 2009a).

The H₄ receptor also appears to be involved in IL-17 production from Th17 cells. Histamine and an H₄R-selective agonist increased IL-17 message and protein secretion from human Th17 cells, and this effect could be blocked by an H₄ receptor antagonist (Mommert et al., 2012). It has also been shown that H₄ receptor antagonists can reduce IL-17 production from PBMC (peripheral blood mononuclear cells) after stimulation (Cowden et al., 2014). The same effect is seen in mice. Stimulation of whole blood with anti-CD3/CD28 and IL-23 led to an increase in IL-17 production in vitro, and this was decreased in blood taken from H₄R-deficient mice or mice treated with an H₄ receptor antagonist (Cowden et al., 2014). Furthermore, it was shown that Th17 cell development in vivo was inhibited in H₄R-deficient mice or mice treated with an H₄ receptor antagonist (Cowden et al., 2014). Finally, a reduction in IL-17 levels via H₄ receptor blockade has been noted in mouse models of asthma, dermatitis, and arthritis (Dunford et al., 2006; Cowden et al., 2010b, 2014). Basophils have been implicated in enhancing Th17 responses in humans, and this effect appears to be mediated by H₂ receptor and H₄ receptor (Wakahara et al., 2012). In human neutrophils, engagement of the H₄ receptor blocked the adhesion-dependent degranulation, indicating a possible anti-inflammatory effect of the H₄ receptor on these cells (Dib et al., 2014).

In human and murine mast cells, the H₄ receptor is not only involved in chemotaxis but also in other functions. H₄ receptor stimulation in murine bone marrow-derived mast cells induced IL-6 production and increased lipopolysaccharide (LPS)-induced IL-6

production via ERK and PI3K activation (Desai and Thurmond, 2011). Stimulation of murine bone marrow-derived mast cells with an H₄ receptor antagonist during the IgE sensitization phase inhibited the degranulation and IgE-induced upregulation of the high affinity IgE receptor Fc ϵ RI (Mirzahosseini et al., 2013). In human cord blood-derived mast cells, histamine and 4-methylhistamine (**17**) induced degranulation and the production of leukotrienes, and these effects were blocked by JNJ-7777120 (**58**) (Jemima et al., 2014). Furthermore, these cells responded to 4-methylhistamine with ERK and PI3K activation as well as the production of a variety of inflammatory mediators such as IL-6 (Jemima et al., 2014). In ex vivo animal models, human mastocytoma cells and bone marrow-derived murine mast cells, H₄ receptor activation resulted in inhibition of renin release via activation of protein kinase C isotype- ϵ and aldehyde dehydrogenase type-2 (Aldi et al., 2014).

The in vitro effects on chemotaxis and mediator release from immune cells suggest that the H₄ receptor should be involved in inflammatory responses. Indeed this has been borne out in several animal models. The first in vivo reports of H₄ receptor activity involved neutrophilia models induced by the TLR ligand zymosan where H₄ receptor antagonists were shown to be anti-inflammatory (Gantner et al., 2002; Thurmond et al., 2004). Effects on neutrophils can also be seen in a rat colitis model where treatment with H₄ receptor antagonists reduced tissue damage, neutrophilia, and tissue TNF α levels (Fogel et al., 2005; Varga et al., 2005). Treatment with JNJ-7777120 was protective in a model of gastric ulceration (Adami et al., 2012). A link between TLR signaling and the H₄ receptor may be a general effect as TNF production upon in vivo administration of LPS has been shown to be reduced in H₄R-deficient mice or upon treatment with H₄ receptor antagonists (Cowden et al., 2013). The role of the H₄ receptor in both innate and adaptive immune responses may explain the protective effect of H₄ receptor antagonists or genetic deficiency in the receptor in mouse models of arthritis (Nent et al., 2013; Cowden et al., 2014).

Eosinophilic inflammation appears also to be mediated by the H₄ receptor. In mouse models of asthma, H₄ receptor antagonists reduced eosinophilia and Th2 responses (Dunford et al., 2006; Deml et al., 2009; Cowden et al., 2010a; Somma et al., 2013). However, the story may not be as straightforward as it first appeared, because a locally administered H₄R/H₂ receptor agonist was protective in another mouse asthma study and these effects may have been mediated via enhanced recruitment of regulatory T cells via the H₄ receptor (Morgan et al., 2007). In another study on EAE, H₄ receptor knockout mice had a worse outcome compared with wild-type controls. This was attributed to altered migration and function of regulatory T cells in the H₄ receptor knockouts (del Rio et al., 2012). Th2

responses can also be impacted in models of cutaneous inflammation. In most acute models driven by hapten application, the H₄ receptor clearly mediated pruritic responses but did not have a role in the acute inflammation (Rossbach et al., 2009; Seike et al., 2010). However, with chronic application the situation appears to change and an H₄ receptor antagonist was anti-inflammatory, whereas an H₄ receptor agonist was proinflammatory (Seike et al., 2010). This may be a result of the switch to a more eosinophilic inflammation with the chronic treatment. Interestingly, the one acute hapten model that is sensitive to H₄ receptor inhibition is the one where even the acute inflammation has a strong eosinophilic component. In this case, treatment with H₄ receptor antagonists were anti-inflammatory and led to a reduction in the number of mast cells and eosinophils in the affected skin (Cowden et al., 2010b). In addition to effects on eosinophils, the H₄ receptor also mediates keratinocyte proliferation, which may explain some of the effects seen in the model (Glatzer et al., 2013). Finally, the combination of H₁ receptor and H₄ receptor antagonists was more effective than either alone in two models of contact dermatitis (Matsushita et al., 2012; Ohsawa and Hirasawa, 2012).

Beyond the role in inflammatory response the H₄ receptor has also been associated with neuronal responses, although this remains controversial (Schneider et al., 2014b). A study analyzed [³⁵S]GTPγS binding and noradrenaline release in human, guinea pig, and mouse cortex (Feliszek et al., 2015). The H₄ receptor agonist 4-methylhistamine (**17**) failed to affect these readouts, whereas the H₃ receptor increased [³⁵S]GTPγS binding and inhibited noradrenaline release. These readouts are limited in their coverage of potential neuronal effects of the H₄ receptor, and so further studies are required. Nevertheless, the H₄ receptor expression has been reported on neurons, suggesting that it can have an effect on sensory signaling. In whole cell clamp recordings of layer IV somatosensory cortex cells from mice, H₄ receptor-induced hyperpolarization has been reported with a single H₄ receptor agonist, antagonist, and respective dose (Connelly et al., 2009); confirmation is required with multiple ligands and a full concentration range. In rat vestibular neurons, treatment H₄ receptor antagonist led to inhibitory effects on the action potential (Desmadryl et al., 2012). In addition it has been shown that the receptor also mediated action potential discharge in human submucosal neurons (Breunig et al., 2007). Single-cell Ca²⁺ imaging studies in mice recently showed that histamine induces a [Ca²⁺]_i increase in a subset of (skin-specific) sensory neurons via activation of the H₄ receptor. Dual activation of H₁ receptor and H₄ receptor on sensory neurons, which in turn results in the excitation of histamine-sensitive afferents, may underlie the sensation of itch (Rossbach et al., 2011). These effects may translate into the nociceptive and antipruritic activities seen in animal models (Bell et al., 2004;

Coruzzi et al., 2007; Dunford et al., 2007; Altenbach et al., 2008; Cowart et al., 2008; Nakano et al., 2009; Rossbach et al., 2009; Yamaura et al., 2009; Cowden et al., 2010b; Hsieh et al., 2010a,b). In both cases the effects of H₄ receptor antagonists appear to be mediated via modulation of neuronal activity. For example, the reduction in pruritic responses in H₄R-deficient mice could not be reconstituted with bone marrow from wild-type animals (Dunford et al., 2007). Furthermore, compound 48/80 was shown to induce pruritic responses by directly activating neurons, and these effects were reduced by H₄ receptor antagonists (Dunford et al., 2007).

Recently, the expression of all four histamine receptors has been demonstrated on microglia, which represents resident immune cells in the brain (Ferreira et al., 2012; Dong et al., 2014). Histamine induced microglia migration and inhibited LPS-induced IL-1β production via the H₄ receptor in one study (Ferreira et al., 2012). In another study, histamine induced TNFα and IL-6 production, which could be blocked by H₁ receptor and H₄ receptor antagonists (Dong et al., 2014). Thus, neuronal functions could also be indirectly affected via histamine influence on microglia.

A number of other functions have been described for the H₄ receptor. One study showed that the administration of histamine increased COX-2 expression and activity, cell proliferation, and vascular endothelial growth factor production in the COX-2-positive colon cancer cell lines HT29 and Caco-2, and treatment with the H₂ receptor or H₄ receptor antagonists prevented these effects (Cianchi et al., 2005). The H₄ receptor has been shown to mediate cell cycle arrest in hematopoietic progenitor cells induced by growth factors (Petit-Bertron et al., 2009). In addition, activation of the receptor appears to inhibit proliferation of several human cancer cell lines (Massari et al., 2011, 2013). The release of adrenocorticotrophic hormone from a mouse pituitary tumor cell line via H₄ receptor activation has also been reported (Meng et al., 2008). Simultaneous activation of H₄ receptor and H₂ receptor has been reported to mediate sickle erythrocyte adhesion to endothelium (Wagner et al., 2006).

In a rat model of postinflammatory visceral hypersensitivity, colitis was induced by trinitrobenzenesulfonic acid, and after healing, visceral sensitivity was measured after administration of JNJ-7777120 (**58**) and/or levocetirizine (**11**) (Deiteren et al., 2014). Visceral sensitivity was reduced by JNJ-7777120 and levocetirizine, the combination of both had a synergistic effect.

E. H₄ Receptor-Selective Ligands

Many known ligands of the H₃ receptor, notably imidazole-containing compounds, also possess significant affinity for the H₄ receptor. These include (*R*)-α-methylhistamine (**33**), imetit (**34**), immepip (**35**), and clobenpropit (**41**), which all act as agonists at the H₄ receptor. In

contrast, the H₃ receptor neutral antagonist thioperamide (**40**) was shown to be an inverse agonist of the H₄ receptor (Oda et al., 2000; Liu et al., 2001a,b; Lim et al., 2005).

1. Agonists. The first described H₄ receptor agonists were methylcyanoguanidine analogs of 2,5-disubstituted tetrahydrofuranylimidazoles. These compounds have moderate affinity for the H₄ receptor and some selectivity over H₃ receptor (Lim et al., 2005). The best example is OUP-16, with a binding K_i of 125 nM for the human H₄ receptor and an 18-fold selectivity over H₃ receptor (Hashimoto et al., 2003).

Although initially developed as a H₂ receptor ligand, 4-methylhistamine (**17**) (K_i = 50 nM) is the most selective H₄ receptor agonist currently reported, with more than 100-fold selectivity over the H₁ receptor, H₂ receptor and H₃ receptor. Structural modification of dimaprit (a nonimidazole, mixed H₂ receptor/H₃ receptor/H₄ receptor ligand; **19**) led to the discovery of VUF-8430 (**57**), a full agonist at the H₄ receptor with around 30-fold selectivity over the H₃ receptor (Lim et al., 2006).

The antipsychotic drug clozapine (**56**) has affinity for a number of GPCRs but also possesses H₄ receptor agonist activity. Minor structural modification of this tricyclic compound led to the identification of VUF-6884, a close analog with good affinity for the H₄ receptor, shown to be more than 300-fold selective over the H₃ receptor (Lim et al., 2006). The aminopyrimidine ligand ST-1006 (**75**) has been characterized as the most potent H₄ receptor agonist reported to date, with a PEC₅₀ of 8.95 (Gschwandtner et al., 2013) (Fig. 15).

2. Antagonists. The indole carboxamide compound JNJ-7777120 (1-[(5-chloro-1*H*-indol-2-yl) carbonyl]-4-methylpiperazine; **58**) was the first published selective nonimidazole H₄ antagonist. It was reported to bind to the human H₄ receptor with high affinity (K_i = 4 nM) and has excellent selectivity over a panel of GPCRs, including the H₁ receptor, H₂ receptor and H₃ receptor (Thurmond et al., 2004). JNJ-7777120 also possesses high affinity for the mouse and rat H₄ receptor (Thurmond et al., 2004), and it has been used extensively as the reference compound to determine the role of H₄ receptor antagonism in a variety of experimental animal models of disease (Stark, 2013).

Based on JNJ-7777120, a range of structurally diverse compound classes has evolved, as represented by the benzimidazole VUF-6002, also known as JNJ-10191584 (**59**) (Terzioglu et al., 2004) and thienopyrrole (**60**) analogs (Venable et al., 2005). Both compounds **59** and **60** demonstrated binding affinities close to that of JNJ-7777120 (Terzioglu et al., 2004; Venable et al., 2005). Similar compounds were published by Pfizer (New York, NY), as represented by compound **61**, where the *N*-methylpiperazine moiety of **59** was replaced by an octahydropyrrolo[3,4-*c*]pyrrole group. This compound has low nanomolar affinity for the human H₄ receptor (Lane et al., 2012). Further benzimidazole-containing

compounds were described in a series of patents from Johnson & Johnson (New Brunswick, NJ) (Arienti et al., 2006; Lee-Dutra et al., 2006; Edwards et al., 2007a,b). The benzimidazole scaffold in these compounds is typically linked to a substituted phenyl or heterocycle. These are then connected by an alkyloxy or alkyl amine chain to a piperidine or (homo)piperazine moiety.

Quinoxaline derivatives such as compound **62** were found to possess excellent affinity for the human H₄ receptor (Edwards and Venable, 2005). Further exploration of the SAR led to the identification of piperazin-1-yl quinoxalines, including VUF-10214 (**63**) and VUF-10148 (**64**), which retained good H₄ receptor potency and demonstrated anti-inflammatory efficacy in a rat model of carrageenan-induced paw edema (Smits et al., 2008).

Aminopyrimidine analogs are the most widely published H₄ receptor antagonists and it was Bayer (Leverkusen, North Rhine-Westphalia, Germany) who first disclosed two series of 2-aminopyrimidine compounds possessing significant H₄ receptor functional activity, as exemplified by compound **65** (Sato et al., 2005). Subsequently, further 2-aminopyrimidine H₄ receptor antagonists were published by Johnson & Johnson (**66**) (Cai et al., 2008), Pfizer (**67**) (Bell et al., 2007), Palau (Palau-solità i Plegamans, Barcelona, Spain) (**68**) (Carceller Gonzalez et al., 2007), UCB (Brussels, Belgium) (**69**) (Raphy et al., 2008), Abbott (**70**) (Altenbach et al., 2008; Cowart et al., 2008), Incyte (Wilmington, DE) (**74**), and academic institutions (Sander et al., 2009; Werner et al., 2010). ZPL-3893787 or formerly PF-3893787 (**67**) has completed phase I studies and is being developed by Ziarco Pharma (Sandwich, UK) as an oral treatment of atopic dermatitis (Liu, 2014). The other clinical stage compound JNJ-39758979 (**72**) significantly reduced histamine-induced itch in healthy human subjects (Kollmeier et al., 2014). INCB38579 (**74**) has demonstrated efficacy in preclinical models of inflammatory pain and pruritus (Shin et al., 2012).

Rotationally constrained analogs of the 2-aminopyrimidine class, including benzofuopyrimidines and benzothienopyrimidines, have also been shown to be potent H₄ receptor antagonists. These compounds have been claimed by Argenta (Harlow, UK), Cellzome (Heidelberg, Germany) (Reid et al., 2007a,b,c), Johnson & Johnson (**71**) (Chavez et al., 2008), and Abbott (**73**) (Altenbach et al., 2008). Compound A-943931 (**73**) has shown efficacy in various animal models of pain, inflammation, and pruritus (Cowart et al., 2008).

JNJ-7777120 (**58**) has been broadly used as standard H₄ receptor antagonist to delineate specific pathophysiological functions of the H₄ receptor. In fact, JNJ-7777120 exhibits an excellent selectivity for the H₄ receptor relative to the H₁ receptor, H₂ receptor and H₃ receptor and numerous other GPCRs (Jablonowski et al., 2003). Most animal studies with JNJ-7777120 are compatible with the notion that the H₄ receptor

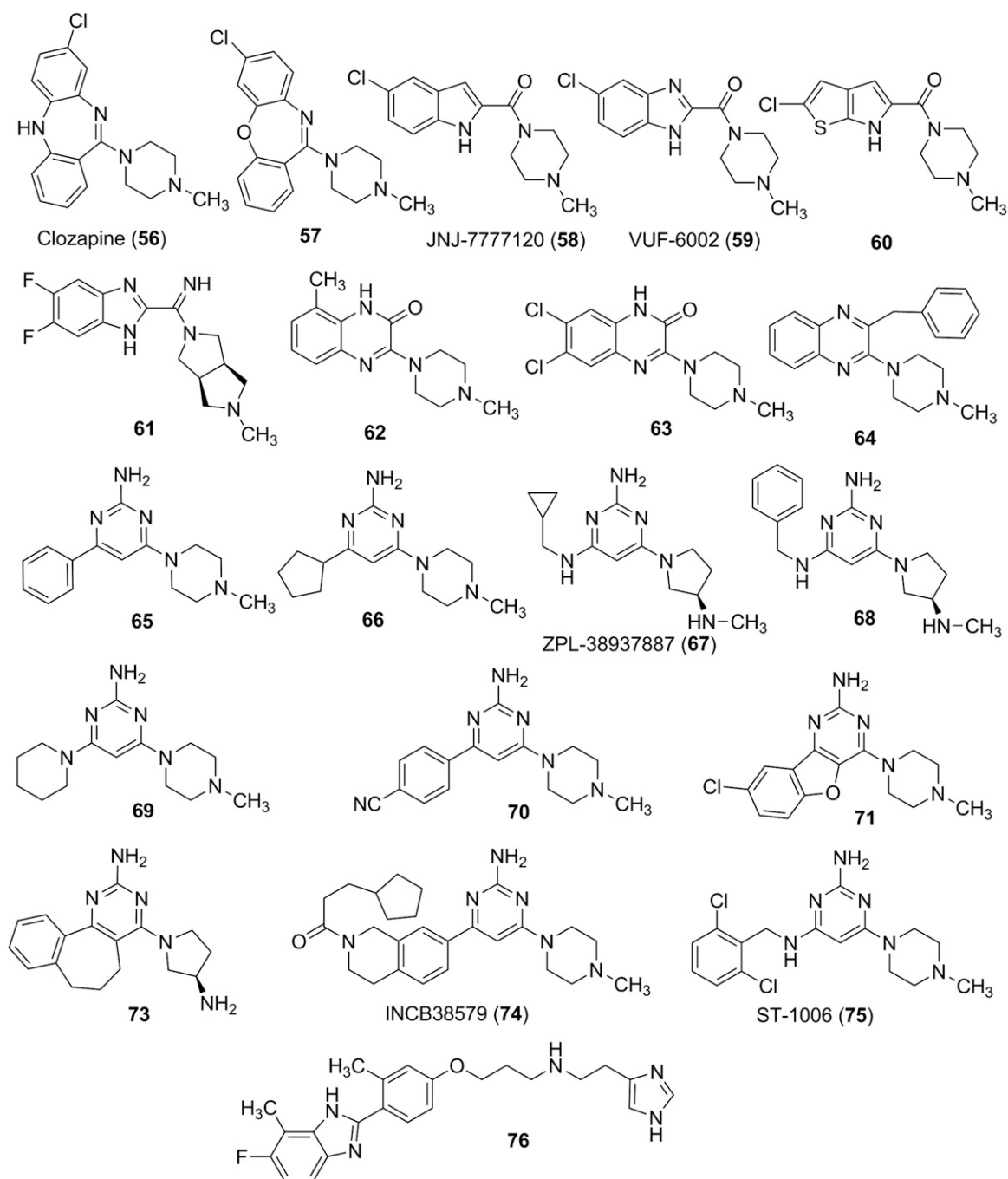


Fig. 15. H₄ receptor ligands.

play a proinflammatory role in bronchial asthma, atopic dermatitis, and pruritus and that H₄ receptor antagonism blocks those proinflammatory effects (Dunford et al., 2006; Deml et al., 2009; Rossbach et al., 2009).

However, the pharmacology of H₄ receptor ligands is not clear cut and well understood and therefore care must be taken when interpreting the results from any single ligand. For example, Schnell et al. (2011) reconstituted H₄ receptor species orthologs from human, rat, mouse, and canine with the G protein heterotrimer

G₁α₂β₁γ₂ plus the regulator of G protein signaling RGS19 in Sf9 insect cell membranes and measured high-affinity steady-state GTPase activity as a parameter for receptor activation. At all four H₄ receptor species orthologs, histamine acted as full agonist. At human H₄ receptor, JNJ-777120 exhibited partial inverse agonistic activity, whereas at the other H₄ receptor species orthologs, JNJ-777120 exhibited partial agonistic activity. Moreover, at canine H₄ receptor, thioperamide displayed weak partial agonism, whereas at human H₄ receptor, the compound was a strong inverse agonist, and at rat and mouse H₄

receptor, thioperamide is a neutral antagonist or very weak inverse agonist. To make matters more complicated, Rosethorne and Charlton (2011) expressed the human H₄ receptor in an osteosarcoma cell line and found that with respect to [³⁵S]GTPγS binding, JNJ-7777120 behaved as a neutral antagonist or very weak inverse agonist. In marked contrast, with respect to translocation of beta-arrestin to the plasma membrane, JNJ-7777120 exhibited strong partial agonistic activity. Moreover, JNJ-7777120 induced a delayed activation of the mitogen-activated protein kinase pathway that is typical for β-arrestin-mediated signal transduction (Luttrell and Gesty-Palmer, 2010).

The reported biased H₄ receptor signaling by JNJ-7777120 has in the meantime been extended to a broader range of benzimidazole analogs (Nijmeijer et al., 2013), but testing a variety of known H₄ receptor ligands has resulted in the identification of biased ligands for both the G protein and β-arrestin pathways (Nijmeijer et al., 2012).

Although data such as these are currently restricted to transfected cell systems and have not been observed in primary cells, it points to the potential complex pharmacology of the H₄ receptor and JNJ-7777120. As with any single ligand, researchers must use a combination of tools including agonist/antagonist pairs, ligands from different chemical classes, and/or knockout animals before making conclusions about the function of the receptor.

Discrepancies are also reported in vivo and in primary cells. In a murine model of allergic asthma, the effects of the H₄ receptor antagonist JNJ-7777120, the H₃ receptor antagonist JNJ-5207852, and the H₃ receptor and H₄ receptor antagonist thioperamide were compared when given during the sensitization phase in ovalbumin-induced allergic asthma (Neumann et al., 2013). After provocation, JNJ-7777120 resulted in reduced serum titers of ovalbumin-specific IgE, inflammatory infiltrations in the lungs, and eosinophils in the bronchoalveolar lavage as previously reported (Dunford et al., 2006). Thioperamide did not completely mimic the results seen with JNJ-7777120 because it only resulted in lower eosinophil counts in the bronchoalveolar lavage; JNJ-5207852 had no effect on the investigated parameters. The apparent disconnect between the results seen with JNJ-7777120 and thioperamide led the authors speculate that JNJ-7777120 could have effects other than blocking the H₄ receptor. However, these differences can also be accounted for by the known nonspecific activity of thioperamide (such as dual H₃ receptor/H₄ receptor antagonism) or differences in pharmacokinetics. In monocytes as native human cells, a study compared the ability of different H₄ receptor agonists (4-methylhistamine [14], UR-PI376, clobenpropit [41], VUF8430, and ST-1006 [75]) in their ability to suppress IFNγ + LPS-induced IL-12 production (Gschwandtner et al., 2013). All agonists had considerable lower potencies in

this assay compared with published data from transfected cell lines, and the effect could be only partially blocked by JNJ-7777120 in the case of 4-methylhistamine, UR-PI376, clobenpropit, and VUF8430 but completely blocked the ST-1006 effect. Finally, a study compared the development of murine autoimmune encephalomyelitis in histidine-decarboxylase knockout mice lacking histamine and knockout mice lacking all four known histamine receptors (Saligrama et al., 2013). Whereas the encephalomyelitis was aggravated in histidine-decarboxylase knockout mice, symptoms were alleviated in H₁ receptor–H₄ receptor knockout mice. The authors speculated that there might be histamine signaling pathways independent of the known H₁ receptor–H₄ receptor.

F. Clinical Potential

Since its discovery at the turn of the millennium the therapeutic utility of targeting the H₄ receptor has been a subject of intense research. It is remarkable that in such a short period of time compounds are already entering clinical development. This has culminated with the first clinical efficacy results being published in 2014.

Effects of H₄ receptor ligand on pruritus have been among the first studied clinically. Histamine has long been known as a mediator that induces itch in normal human skin, and this pruritic response was shown to be further enhanced in patients with atopic dermatitis (Ikoma et al., 2003). In a mouse model of experimental pruritus, it was shown that both histamine and 4-methylhistamine (17) produced significantly less scratching in H₄ receptor knockout mice when compared with wild-type animals (Dunford et al., 2007). In the same study, the histamine-induced pruritic response in wild-type mice was significantly reduced after oral treatment with the selective H₄ receptor antagonist JNJ-7777120 (58). Administration of an H₂ receptor antagonist, an H₃ receptor antagonist, or the peripherally restricted H₁ receptor antagonist fexofenadine (13) produced no reduction in the scratching response. Interestingly, the CNS-penetrant H₁ receptor antagonist diphenhydramine (6) demonstrated some antipruritic activity, and the combination of diphenhydramine and JNJ-7777120 resulted in the total ablation of the histamine-induced pruritic response (Dunford et al., 2007).

The antipruritic property of H₄ receptor antagonism in animal models appears to be broad based. Significant reduction in the pruritic response by JNJ-7777120 has been observed after challenges with allergen and compound 48/80 (Dunford et al., 2007), substance P (Yamaura et al., 2009), the haptens 2,4-dinitrochlorobenzene and toluene-2,4-diisocyanate (Rossbach et al., 2009), and fluorescein isothiocyanate (Cowden et al., 2010b). There is also increasing human evidence, including expression of the H₄ receptor on skin mast cells

(Lippert et al., 2004) and epidermal dendritic cells (Bäumer et al., 2008; Dijkstra et al., 2008). H₄ receptor agonists have been shown to induce the production of IL-31 in PBMC and Th2 cells, a cytokine that is linked to the induction of pruritus in atopic dermatitis and the effect was blocked by JNJ-7777120 (Sonkoly et al., 2006; Grimstad et al., 2009; Gutzmer et al., 2009). The antipruritic effects of H₄ receptor antagonist combined with anti-inflammatory effects in Th2-driven dermatitis models (Cowden et al., 2010b; Seike et al., 2010) indicate that compounds targeting the receptor should be beneficial in a number of pruritic conditions, such as atopic dermatitis and urticaria.

The preclinical findings have now been validated in the clinic using JNJ-39758979 (**72**), a potent and selective H₄ receptor antagonist (Thurmond et al., 2014a). This compound showed excellent preclinical safety in rat and monkey 6-month toxicity studies, and an oral formulation was well tolerated, with the exception of nausea, in a phase I clinical study with healthy volunteers (Thurmond et al., 2014a). In a double-blind study the effect of a single dose of JNJ-39758979 (**72**), cetirizine (**11**), or placebo was tested on histamine-induced itch, wheal, and flare reactions. JNJ-39758979 significantly reduced itching but did not affect wheal and flare reactions, whereas cetirizine reduced both itch and wheal and flare (Kollmeier et al., 2014).

This clinical result points to therapeutic potential in pruritic conditions known to be mediated by histamine such as acute urticaria, allergic rhinitis, and allergic conjunctivitis. Furthermore, the combination of the human and preclinical data supports the potential in other pruritic conditions such as atopic dermatitis and psoriasis.

The clinical effects on histamine-induced pruritus along with preclinical data showing a role of for the H₄ receptor in inflammation suggest that inflammatory skin disease may be attractive indications for ligands of the receptor. Preclinical data have shown that antagonism of the receptor is efficacious in several dermatitis models (Cowden et al., 2010b; Seike et al., 2010; Matsushita et al., 2012; Ohsawa and Hirasawa, 2012; Thurmond et al., 2014a). In addition, the receptor has been shown to mediate inflammatory activity of many cell types implicated in atopic dermatitis and psoriasis.

Allergic airway diseases, such as asthma and allergic rhinitis, have also been suggested to be potential indications for H₄ receptor ligands. Histamine has long been documented to be released in the human lung during an asthmatic response (Casale et al., 1987). However, H₁ receptor antagonists are only weakly efficacious in treating this inflammatory airway disease (Simons, 1999; Thurmond et al., 2008), and there is little evidence supporting a clinical benefit with H₂ receptor or H₃ receptor antagonists. Although the lack of effect may imply that histamine is not important in asthma, this

seems unlikely given its bronchoconstrictive and proinflammatory actions. Instead the lack of efficacy of H₁ receptor antagonists may indicate the involvement of another histamine receptor. Certainly the expression of the H₄ receptor on immune cell types known to be involved in asthma (such as eosinophils, mast cells, T lymphocytes, and dendritic cells), coupled with its involvement in inflammatory processes including chemotaxis and cytokine production, support the concept that targeting this receptor may provide therapeutic benefits.

In addition to data derived from cellular expression and in vitro functional studies, results obtained from animal models have provided further evidence to support a role for the H₄ receptor in modulating airway inflammation. After allergen challenge of sensitized H₄ receptor KO mice, there was a significant decrease in infiltrating lung eosinophils and lymphocytes compared with sensitized wild-type animals (Dunford et al., 2006). Ex vivo restimulation of T lymphocytes from the H₄R-deficient animals showed significant decreases in a range of proinflammatory cytokines and indicated that the receptor was mediating Th2 responses in this model (Dunford et al., 2006). This dampening of airway inflammation has also been observed after the administration of H₄ receptor antagonists in a number of animal models (Dunford et al., 2006; Deml et al., 2009; Cowden et al., 2010a; Thurmond et al., 2014a). In addition to the anti-inflammatory effects in the lung, JNJ-7777120 was also shown to improve lung function in these mouse models (Cowden et al., 2010a). In contrast, intratracheal administration of the H₄ receptor agonist 4-methylhistamine was found to be protective in a mouse model of allergic asthma, potentially through recruitment of regulatory T lymphocytes (Morgan et al., 2007). However, the 4-methylhistamine data are difficult to interpret, because in addition to its agonist effects on the H₄ receptor, 4-methylhistamine (**17**) also exhibits agonist effects on the H₂ receptor (Black et al., 1972). Although H₁ receptor antagonists per se do not play a role in bronchial asthma, it is possible that there are effects when combined with H₄ receptor antagonists. Specifically, when applied alone in the sensitization phase, the H₁ receptor antagonist mepyramine exhibited no beneficial effect on eosinophilia in the bronchoalveolar lavage fluid in a mouse asthma model (Deml et al., 2009). However, mepyramine (**8**) potentiated the therapeutic effects of JNJ-7777120 (**58**) in this disease model. Based on these data, the development of dual H₁ receptor/H₄ receptor antagonists may be desirable. But again and by analogy to the data with 4-methylhistamine (Morgan et al., 2007), the situation may be more complex, particularly when applied during the provocation phase, because mepyramine (**8**) antagonized the effects of JNJ-7777120 (Beermann et al., 2012a).

The H₄ receptor may also play a role in mediating upper airway inflammation. In patients with chronic rhinosinusitis, there is a significant increase in the

level of H_4 receptor expression in nasal polyp tissue when compared with normal nasal mucosal tissue (Jokuti et al., 2007). In a mouse model of allergic rhinitis, JNJ-777120 (**58**) was effective in significantly reducing various upper airway inflammatory symptoms, including sneezing and nasal rubbing, when the compound when given either orally or intranasally (Takahashi et al., 2009). Clinical studies in asthma and allergic rhinitis have been reported for the H_4 receptor antagonists JNJ-39758979 (**72**), UR-63325, and PF-03893787 (now known as ZPL-3893787 [**67**]), so the question on whether H_4 receptor antagonism would provide therapeutic benefits in inflammatory airway diseases may soon be answered once the data from these studies are published.

In addition to inflammatory diseases, a role for the H_4 receptor in nociception was recently suggested. Both JNJ-777120 (**58**) and its benzimidazole analog VUF6002 (**59**) were effective in increasing paw withdrawal latency in a rat model of carrageenan-induced thermal hyperalgesia (Coruzzi et al., 2007). Additional work has shown that this compound was as efficacious as the nonsteroidal anti-inflammatory drug diclofenac in this model (Hsieh et al., 2010a). Similar effects have also been shown with other H_4 receptor antagonists in this model where once again the maximum effect was similar to diclofenac (Altenbach et al., 2008; Cowart et al., 2008; Liu et al., 2008). The amino-pyrimidine H_4 receptor antagonist A-943931 (**73**) was also effective in the carrageenan model, as well as in a spinal nerve ligation model of neuropathic pain (Altenbach et al., 2008). Effects have also been seen in more chronic models. JNJ-777120 (**58**) was efficacious in a subchronic inflammatory pain model induced by complete Freund's adjuvant (Hsieh et al., 2010a). Effects were also seen in a skin incision model of postoperative pain using mechanical allodynia as a readout (Hsieh et al., 2010a). In this case, the highest dose of JNJ-777120 yielded an effect approaching that of morphine. The compound was also tested in model of osteoarthritis joint pain (Hsieh et al., 2010a). This model uses intra-articular injection of sodium monoiodoacetate, and pain was assessed by the hindlimb grip force. JNJ-777120 was delivered 20 days after sodium monoiodoacetate injection 30 minutes before the assessment. The compound was efficacious and improved the grip force by 47% compared with a 62% improvement with celecoxib. H_4 receptor antagonists have also shown efficacy in models of neuropathic pain. In pain models in rats induced by chronic constriction of the sciatic or spinal nerve, JNJ-777120 showed a reversal that was better than that observed with gabapentin (Hsieh et al., 2010a). Furthermore, the effect was maintained upon dosing for 8 days, indicating that no tolerance development (Hsieh et al., 2010a). Other H_4 receptor antagonists have also shown activity in this model (Cowart et al., 2008). Although the mechanism of action of these antinociceptive effects are not clear, the

recent observation of H_4 receptor expression in the spinal cord, dorsal root ganglion, and certain regions of the brain may offer an explanation (Strakhova et al., 2009b).

In conclusion, the H_4 receptor has emerged as a novel and attractive drug target for a range of disease indications, in particular in disorders associated with inflammation. However, there are still many open questions regarding the function of the receptor. Key among these are the exact expression profile of the receptor and the function, if any, in the nervous system. The recent advancement of H_4 receptor compounds into clinical development will undoubtedly aid our understanding of therapeutic utilities in targeting this newest member of the histamine receptor family.

VI. Other Responses to Histamine

A. Histamine-Gated Channels

Ionotropic histamine receptors are common in mollusks and arthropods but have not been unequivocally identified in vertebrates (McCaman and Weinreich, 1985; Gisselmann et al., 2002). The ionotropic histamine receptor in invertebrates is a chloride channel related to the glycine and the $GABA_A$ receptor (Fleck et al., 2012). In vertebrates it may turn out to be a $GABA_A$ -type receptor with a particular subunit composition. Among the many sites for allosteric modulators of the $GABA_A$ receptor there may also be a histamine-sensitive example. Saras et al. (2008) reported that histamine can directly open homomultimeric channels composed of $GABA_A$ receptor β -subunits in which GABA is only a weak partial agonist in *Xenopus* oocytes (Fig. 16A). In heteromultimeric channels composed of $\alpha_1\beta_2$ - or $\alpha_1\beta_2\gamma_2$ -subunits histamine is not an agonist but potentiates the GABA response. These effects have yet to be shown in native neurons.

The axon varicosities of aminergic, including histaminergic, neurons rarely form classic synapses in vertebrates and, apart from nicotinic ACh and 5HT₃ receptors, the biogenic amines act on metabotropic receptors. Nevertheless there are indications for histamine-gated chloride channels in hypothalamus (Hatton and Yang, 2001) and thalamus (Lee et al., 2004) on oxytocin neurons in the supraoptic nucleus, such a conductance is blocked by the chloride channel blocker picrotoxin (not the $GABA_A$ antagonist bicuculline) and H_2 receptor antagonists, not mediated by a G protein. Stimulation of histamine neurons evokes fast inhibitory postsynaptic potentials (IPSPs) that reverse at the chloride equilibrium (Fig. 16B). Hatton and Yang (2001) suggested an ionotropic action and ruled out GABA release from histaminergic axons. Because histamine neurons express GABA, GABA release could have been responsible for these IPSPs.

GABAergic interneurons in the thalamus are surrounded by histaminergic fibers and histamine evokes an inhibitory chloride conductance mediated by a H_2 -related receptor but not cyclic AMP (Lee et al., 2004). GABAergic

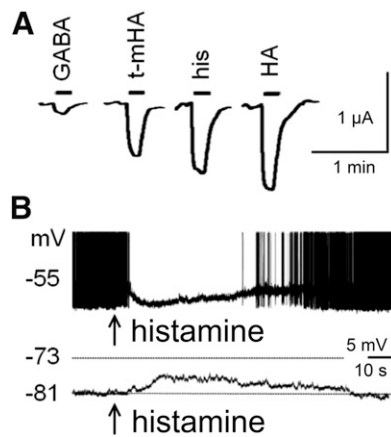


Fig. 16. Histamine gating chloride-channels. (A) Responses of artificially expressed GABA_A receptor β_3 -homomeric channels in xenopus oocytes to GABA, tele-methylhistamine, histidine, and histamine all at 3 mM. (B) Thalamic GABAergic neuron is inhibited and hyperpolarized by histamine in a slice from ferret brain. An increased Cl⁻-conductance (reversal potential -73 mV) displays H₂ receptor pharmacology, see text. Modified from Lee et al. (2004) and Saras et al. (2008) with permission.

activity of imidazole compounds (Haas et al., 1973), in particular imidazole-derived H₂R-antagonists (Lakoski et al., 1983), has been described. Unequivocal evidence for histaminergic IPSPs mediated by chloride currents has been obtained in paired recordings from the histaminergic C2 neuron and a follower neuron in *Aplysia* (McCaman and Weinreich, 1985) (Fig. 17).

B. Allosteric Modulation of N-Methyl-D-Aspartate Receptor

A second-messenger-mediated modulation of ionotropic receptors is common for several transmitters: facilitation of N-methyl-D-aspartate (NMDA) receptors through PKC and a reduction of the Mg²⁺-block have been described as a result of H₁ receptor activation (Payne and Neuman, 1997). However, histamine also directly facilitates NMDA

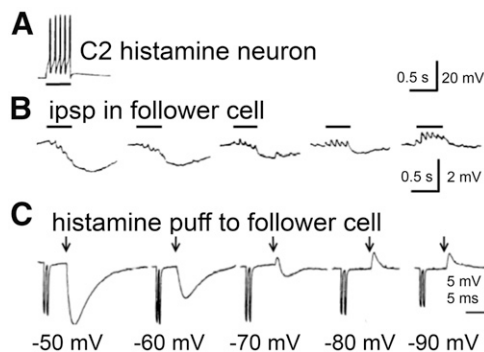


Fig. 17. Ionic mechanism of histaminergic inhibitory postsynaptic potentials (ipsp) in aplysia. Paired recording in the histaminergic C2 neuron from aplysia and a follower neuron. Five action potentials are elicited (A) and the response is registered at different voltage levels (B, from -50 to -90 mV). Histamine is also puffed on the follower neuron at these different voltage levels (C). A fast component reverses at the equilibrium potential for Cl⁻, between -60 and -70 mV, a slow component near -90 mV, close to the K⁺-equilibrium potential. Modified from McCaman and Weinreich (1985).

receptors and enhances excitatory transmission (Bekkers, 1993), likely through their polyamine modulatory site (Vorobjev et al., 1993). This action is occluded by spermidine and is pH sensitive (Saybasili et al., 1995; Yanovsky et al., 1995). In a slightly acidified environment (pH, 7.0), but not at pH 7.4, the late NMDA component of extra- and intracellularly registered excitatory postsynaptic potentials in hippocampal slices is enhanced by histamine (Fig. 18). Such shifts in pH occur during intense nervous discharges, e.g., during seizures or after tetanic stimulation, and in hypoxic conditions. The effect is not mediated by any of the known histamine receptors but can be mimicked by the histamine metabolite 1-methyl-histamine and is selective for the GluN2B subunit of the NMDA receptor (Williams, 1994), which plays a central role in synaptic plasticity. The H₃ receptor antagonists clobenpropit and iodophenpropit have been identified as NMDA-antagonists selective for the GluN2B subunit (Hansen et al., 2010). Histamine also potentiates NMDA-induced [³H]noradrenaline release from hippocampal synaptosomes through an allosteric site distinct from the polyamine site (Faucard et al., 2006). An action of the diamine histamine on the polyamine site of the NMDA receptor may have been predicted from the cross-reaction histamine-spermidine, jeopardizing the early attempts to label histaminergic neurons through fluorescence histology that was available for the other biogenic amines (Green, 1964).

VII. Future Perspectives

Histamine pharmacology is as exciting now as it was back in the early 1970s when there was only one histamine receptor. Recent advances in our knowledge and understanding of histamine pharmacology, with the identification of the H₃ and H₄ receptors and their isoforms over the last decade and the solving of the H₁ receptor structure in 2011, bode well for potential new improved “antihistamines” and future clinical exploitation of these newer histamine receptors. The spectrum of physiologic and pathophysiological roles of histamine

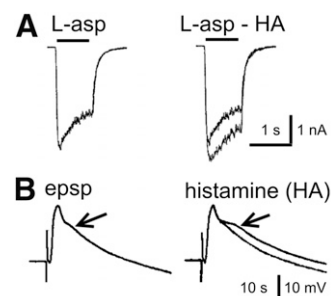


Fig. 18. Histamine potentiates NMDA current. (A) Potentiation of NMDA-current in whole cell clamp with 1-second application of L-aspartate. (B) NMDA component (arrows) of excitatory postsynaptic potential (epsp) in hippocampal pyramidal cell. Modified from Vorobjev et al. (1993) and Yanovsky et al. (1995).

has been expanded profoundly over the last decade, with growing evidence in feeding behaviors, sleep physiology, cognitive function, fear memory, pain physiology for the H₃ receptor, and chronic inflammation, autoimmune function, gastrointestinal endocrine and salivary exocrine function, pain and itch biology, diabetic nephropathy, and cancer biology for the H₄ receptor.

There is still much to understand. The full therapeutic potential of H₃ receptor and H₄ receptor ligands is just starting to emerge as clinical trial data are published. Furthermore, being the newest histamine receptor, there are many outstanding questions with regard to the characterization of the H₄ receptor. In particular it is still not completely clear as to the full complement of cells that express the receptor and whether the receptor has functions beyond inflammation such as in the central or peripheral nervous systems. In addition there is much left to learn about all four receptors with regard to the physiologic and pharmacological relevance of functional selectivity, constitutive activity, splice variants, and oligomerization of the histamine receptor family. Because numerous receptor (hetero)oligomerizations and receptor crosstalks have been reported, one may speculate on the functional properties of numerous compounds with a combined or multitargeted profile with in vivo application and its adoptive processes.

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Authorship Contributions

Wrote or contributed to the writing of the manuscript: Panula, Chazot, Cowart, Gutzmer, Leurs, Liu, Stark, Thurmond, Haas.

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