HISTAMINE RECEPTORS

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Introduction

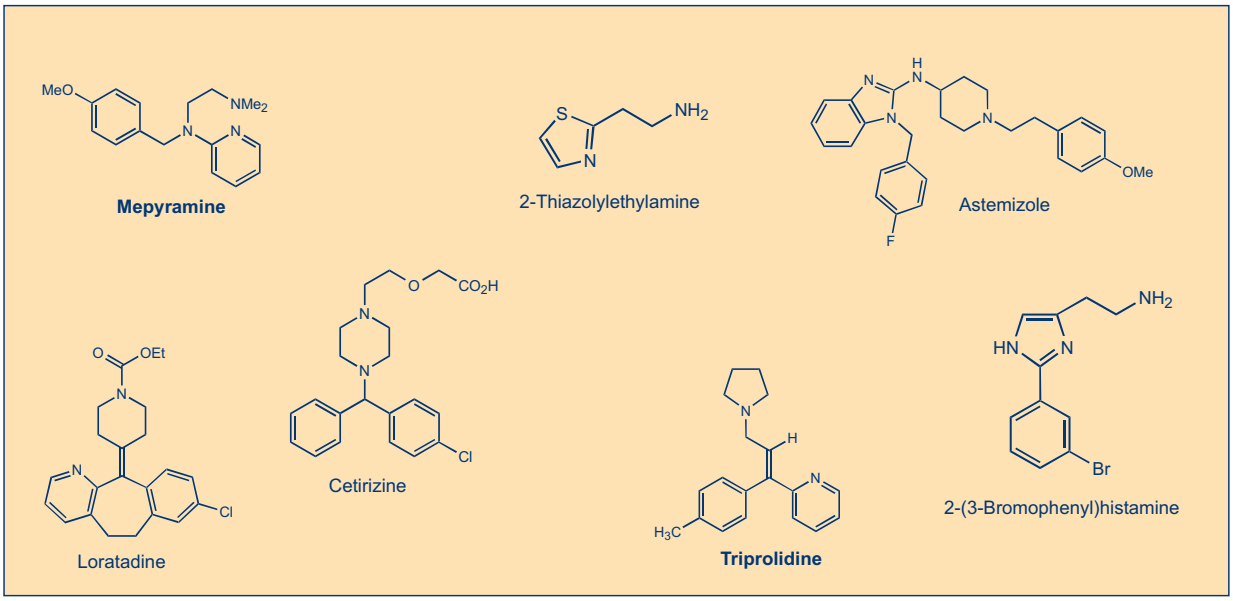
Histamine is one of the aminergic neurotransmitters, playing an important role in the regulation of several (patho)physiological processes. In the mammalian brain histamine is synthesized in a restricted population of neurons located in the tuberomammillary nucleus of the posterior hypothalamus.[1] These neurons project diffusely to most cerebral areas and have been implicated in several brain functions (e.g. sleep/wakefulness, hormonal secretion, cardiovascular control, thermoregulation, food intake, and memory formation).[1] In peripheral tissues histamine is stored in mast cells, basophils, enterochromaffin cells and probably also in some specific neurons. Mast cell histamine plays an important role in the pathogenesis of various allergic conditions. After mast cell degranulation, release of histamine leads to various well-known symptoms of allergic conditions in the skin and the airway system.[2] Based on these observations histamine is considered as one of the most important mediators of allergy and inflammation.

Pharmacology of the Histamine Receptor Subtypes

The advent of molecular biology techniques has greatly increased the number of pharmacologically distinct receptor subtypes in the biogenic amine field, yet the pharmacological definition of the three distinct histamine receptor subtypes by the pioneering work of Ash and Schild,[3] Black *et al* [4] and Arrang *et al* [5] has still not been challenged by gene cloning approaches.

Until the seventies, histamine research completely focused on the role of histamine in allergic diseases. This intensive research resulted in the development of several potent "antihistamines" (e.g. mepyramine), which were useful in inhibiting certain symptoms of allergic conditions.[6] The observation that these "antihistamines" did not antagonise all histamine-induced effects (e.g. at the stomach and the heart), led Ash and Schild in 1966 to propose histamine H_1 and H_2 receptor subtypes.[3] This hypothesis became generally accepted when Black *et al* [4] succeeded in the synthesis of a series

Figure 1. Chemical structures of some H_1 receptor agonists and antagonists



(bold text denotes compounds available from Tocris)

of new compounds (e.g. burimamide, cimetidine), which were able to block the effects of histamine on the stomach and the heart. These H_2 receptor antagonists proved to be very useful in the therapy of gastric ulcers. In recent years it became apparent that histamine also functions as a neurotransmitter.[1] As with many other neurotransmitter systems, a presynaptic receptor for histamine (H_3) exists as well.[5] This receptor subtype regulates the release and synthesis of histamine (autoreceptor), but is also involved in the regulation of the release of many other important neurotransmitters, such as noradrenaline, dopamine, serotonin and acetylcholine (heteroreceptor).[7]

Selective Ligands for the Three Histamine Receptor Subtypes

For all three receptor subtypes selective agonists and antagonists are available.

H_1 Receptors

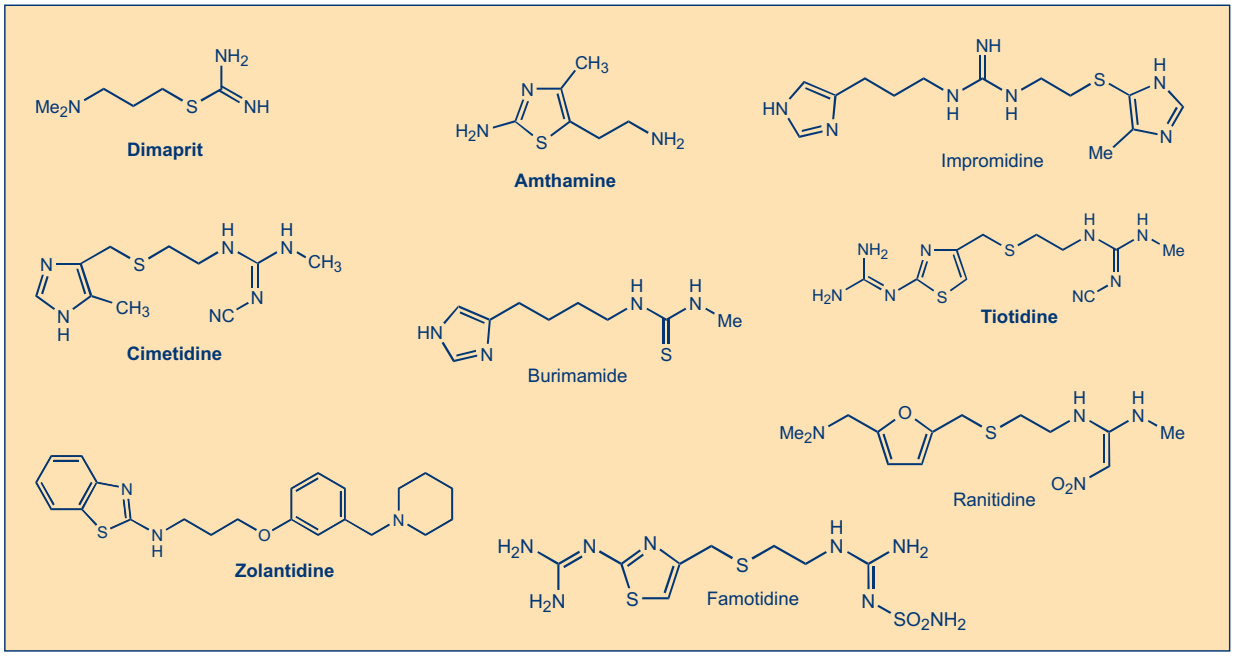
Modification of the imidazole moiety of histamine has been the most successful approach for obtaining selective H_1 agonists (figure 1). The presence of the tautomeric N^{π}-N^{τ} system of the imidazole ring is not obligatory, as reflected by the selective H_1 agonists 2-pyridylethylamine and 2-thiazolylethylamine. Substitution of the imidazole ring at the 2-position leads to relatively selective H_1 agonists. For example, 2-(*meta*-halogenated) phenylhistamines are relatively potent H_1 receptor agonists at the guinea-pig ileum;[8] however, these compounds act as partial agonists in other systems.[9] A wide array of potent and selective H_1 antagonists are available.[6] Compounds such as mepyramine (also called pyrilamine) and triprolidine (figure 1) are highly potent H_1 antagonists and very useful tools for pharmacological investigations. [^{3}H]-mepyramine is, for example, successfully used as an H_1 receptor radioligand.[10] These so-called classical "antihistamines" easily penetrate the brain and are therefore also useful in *in vivo* studies. Clinically, the CNS penetration of these drugs causes sedation. Elimination of the blood-brain-barrier passage by some minor structural modifications (figure 1) has resulted in many new, non-sedating H_1 antagonists (e.g. cetirizine, astemizole or loratadine), that are currently successfully marketed to treat allergic conditions.[6]

H_2 Receptors

The first selective H_2 receptor agonist, dimaprit, was found during a search for H_2 receptor antagonists in a series of isothiourea derivatives. Dimaprit is a relatively selective H_2 receptor agonist; it is almost as active as histamine at the H_2 receptor, but hardly displays any H_1 receptor agonism[11] and is a moderate H_3 receptor antagonist.[12] Recently, amthamine (2-amino-5-(2-aminoethyl)-4-methylthiazole), a rigid dimaprit analog (figure 2), has been developed. This compound combines a high H_2 receptor selectivity with a potency which is slightly higher compared to histamine, both *in vitro* and *in vivo*.[13, 14] An H_2 receptor agonist that is also more potent than histamine is the guanidine derivative impromidine (figure 2). This ligand actually combines a rather high H_2 receptor affinity with a reduced efficacy. Impromidine also shows moderate and potent antagonistic activity at the H_1- and the H_3 receptor respectively.[5, 15]

The finding that N^{α}-guanylhistamine acts as a partial H_2 agonist in a gastric acid secretion test led to the development of the relatively weak H_2 antagonist burimamide (figure 2), which was a good lead for the development of clinically useful H_2 receptor antagonists.[4] Subsequently, many compounds with H_2 receptor antagonistic properties, such as cimetidine, have been

Figure 2. Chemical structures of some H_2 receptor agonists and antagonists



(bold text denotes compounds available from Tocris)

developed.[16, 17] Most of these H_2 blockers can be considered as having small variations on a general structure. The 4-methylimidazole moiety of cimetidine can easily be replaced by other heterocyclic groups (figure 2). Replacement by a substituted furan- (e.g. ranitidine) or thiazole ring (e.g. tiotidine and famotidine) leads to compounds that are usually more potent at the H_2 receptor compared to cimetidine. Moreover, the replacement of the imidazole moiety also eliminates the undesired inhibition of cytochrome P-450.[17] The potent H_2 antagonists tiotidine and iodoaminopotentidine are successfully used as tritiated and iodinated radioligands for the H_2 receptor respectively.[10] The newly developed brain-penetrating H_2 antagonist zolantidine is an important tool for *in vivo* CNS studies.[18]

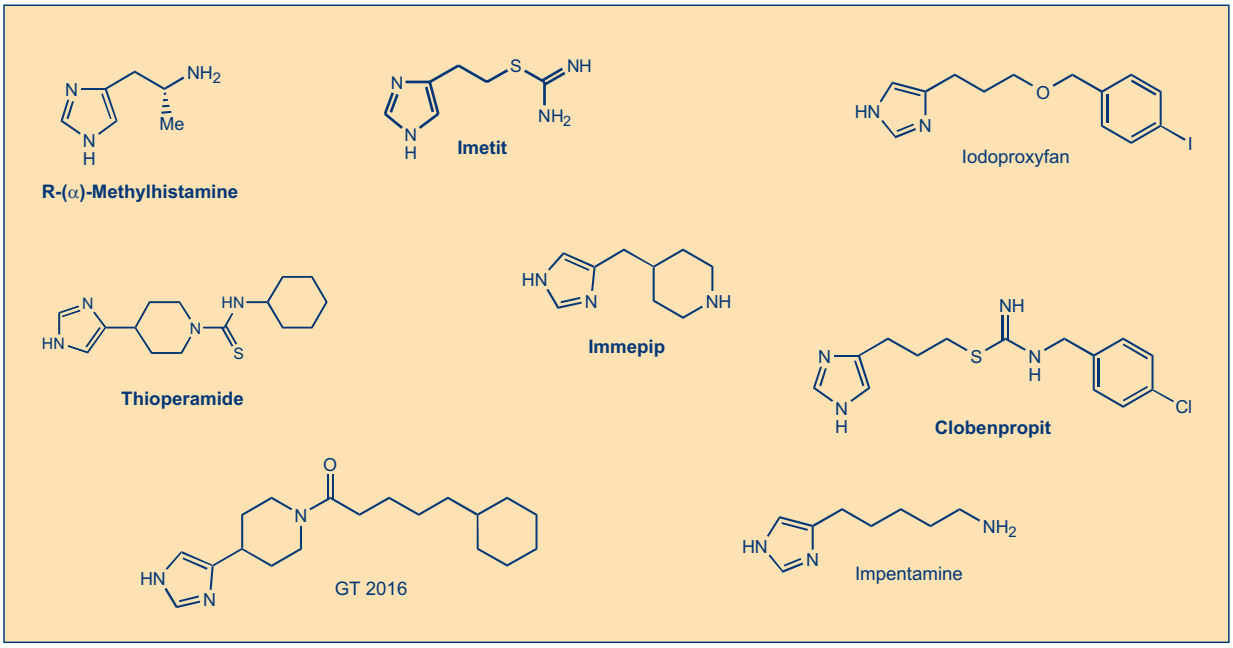
Very recently, the H_2 receptor was reported to be spontaneously active in transfected CHO cells.[19] Based on this concept, the H_2 antagonists were reclassified; cimetidine, ranitidine and famotidine are in fact inverse agonists, whereas burimamide acts in this model system as a neutral antagonist.[19]

H_3 Receptors

At the histamine H_3 receptor, histamine itself is a highly active agonist. Mono- or dimethylation of the terminal amino function results in compounds that are more active and H_3 selective with regard to H_1 and H_2 receptors, than histamine. Methylation of the α-carbon atom of the ethylamine sidechain drastically increases the potency at the H_3 receptor. This increased activity resides completely in the R-isomer; the corresponding S-isomer is approximately 100-fold less potent. Since the methylation leads to highly reduced activity at both the H_1- and H_2 receptor, R-(α)-methylhistamine (figure 3) is a very selective agonist at the H_3 receptor. In combination with its less active S-isomer, this compound has proven to be highly useful for the pharmacological characterisation of H_3 receptor-mediated effects.[12] Tritiated forms of N^{α}-methylhistamine and R-(α)-methylhistamine are currently available as radiolabelled agonists for the H_3 receptor.[12] For potent H_3 agonism, the amine function of histamine can be replaced by an isothiourea group, as in imetit (figure 3). Imetit is also very active *in vitro* and *in vivo,*[20-22] as is R-(α)-methylhistamine. The amine function can also be incorporated in ring structures to produce compounds such as immepip (figure 3). This compound again, is effective *in vitro* and *in vivo.*[23] Moreover, whereas R-(α)-methylhistamine shows some H_1 and α_2 agonistic activity and imetit acts as a 5-HT_3 agonist,[24-26] immepip is devoid of these activities.[25]

Various H_2 receptor selective agents are also rather potent H_3 receptor antagonists.[5] The moderately active H_2 antagonist burimamide (pA_2 = 5.1) is an effective H_3 antagonist (pA_2 = 7.2), and some H_2 agonists (impromidine and dimaprit) are also active as H_3 receptor antagonists.[5] The distinct pharmacology of the H_3 receptor was confirmed by the development of the prototypic H_3 receptor antagonist thioperamide (figure 3).[27] This compound is active in various *in vitro* H_3 receptor assays but shows some 5-HT_3 receptor antagonism.[26] Thioperamide penetrates the CNS and has been used in several *in vivo* studies. Based on the H_3 receptor agonist imetit, the highly potent antagonists clobenpropit (figure 3) and iodophenpropit were developed.[22] These compounds also show some 5-HT_3 receptor antagonism[26] and do not readily penetrate the CNS.[28] Recently, a variety of other potent H_3 receptor antagonists have been described, including impentamine, GT2016 and iodoproxyfan (figure 3).[29] Consequently, various antagonists have been described as radioligands for the H_3 receptor (e.g. [^{125}I]-iodophenpropit and [^{125}I]-iodoproxyfan).[30, 31]

Figure 3. Chemical structures of some H_3 receptor agonists and antagonists



(bold text denotes compounds available from Tocris)

Molecular Biology of Histamine Receptors

Both the histamine H_1 and H_2 receptor belong to the large family of G-protein coupled receptors (GPCRs). The cDNA encoding a bovine H_1 receptor protein was cloned in 1991 after an expression cloning strategy in Xenopus oocytes.[32] The deduced amino acid sequence revealed a 491 amino acid protein of 56 kDa. Using the cDNA sequence encoding the bovine H_1 receptor, the cDNA sequences and intronless genes encoding the rat,[33] guinea-pig,[34, 35] human[36-39] and mouse[40] H_1 receptor proteins were cloned soon thereafter. The proteins are slightly different in length, highly homologous and do not show major differences in pharmacology. Analysis of the 5′-flanking region of the human, rat and guinea-pig gene[33, 34, 36] resulted in the identification of several DNA-binding motifs, including potential glucocorticoid responsive elements. The human H_1 receptor gene resides on chromosome 3.[41]

Gantz *et al* [42] were the first to clone a cDNA encoding a 359 amino acid H_2 receptor. Using degenerate primers based on the known sequence similarity of various GPCRs, the H_2 receptor sequence was obtained from canine gastric parietal cDNA by PCR. Soon thereafter, the intronless genes encoding the rat,[43] human,[44] guinea-pig[45] and mouse[46] H_2 receptor were cloned by means of homology screening. As for the H_1 receptor, the receptor proteins are slightly different in length, but do not show major pharmacological differences. Identification of the promotor region of the human H_2 receptor gene revealed the existence of regulatory transcription sites and regions displaying stimulatory and inhibitory effects on gene expression monitored in a luciferase assay.[47] Recent studies have indicated that the human H_2 receptor gene resides on chromosome 5.[45] Interestingly, several polymorphisms have been found in the human H_2 receptor gene[48] and one of the mutations has been linked to schizophrenia.[49]

Although the genetic information for the H_1 and H_2 receptor has been available for some years now, as yet no information on the primary structure of the H_3 receptor is known.

Signal Transduction of the Histamine Receptors

The histamine H_1 receptor is associated with the phospholipase C-catalyzed formation of inositol 1,4,5-triphosphate (IP_3) and 1,2-diacylglycerol (DAG). Histamine induces production of inositol phosphates in several tissues (including brain, airway, intestinal and vascular smooth muscle[10]) via a pertussis toxin-insensitive G-protein. Although the G-protein probably belongs to the $G\alpha_q/G\alpha_{11}$ family, the actual nature of the pertussin toxin-insensitive G-protein remains unclear. Since Ca^{2+} is involved in the regulation of many cellular functions, the increase of the intracellular Ca^{2+} concentration following H_1 receptor stimulation can explain a variety of cellular responses, such as nitric oxide production, cAMP and cGMP accumulation and phospholipase A_2 and phospholipase D activation.[10] Yet, studies with G-protein toxins and in calcium-free medium indicate that both the H_1 receptor-mediated activation of phospholipase A_2 and cAMP elevation are also mediated by an unknown, secondary mechanism (G-protein mediated?).

The histamine H_2 receptor is coupled to the adenylate cyclase system in a variety of tissues (e.g. brain, stomach, heart, gastric mucosa, lung).[10] Moreover, cell lines transfected with the cloned H_2 receptor genes showed an H_2 receptor-mediated increase of cAMP.[50-52] Although coupling of the H_2 receptor to adenylate cyclase is well accepted, some findings argue against a universal role of cAMP. New signalling pathways have recently been described for the H_2 receptor. In differentiated HL-60 cells and CHO or HEPA cells transfected with the H_2 receptor cDNA, an H_2 receptor-mediated increase of the intracellular Ca^{2+} concentration and/or IP_3 levels was observed.[52-56] Moreover, in CHO cells expressing the rat H_2 receptor, activation of the H_2 receptor resulted in an inhibition of the release of arachidonic acid induced by either constitutive purinergic receptors or a Ca^{2+}-ionophore,[51] as well as an increase in cAMP. These new signal transduction pathways are both regulated via unknown, cAMP-independent pathways.

The H_3 receptor is also thought to belong to the superfamily of G-protein coupled receptors. From both functional and binding studies an interaction with a G-protein is suggested.[10] The concept of G-protein involvement is further strengthened by a recent study[57] showing a pertussis toxin sensitive stimulation of [^{35}S]-GTPγS binding in rat cortical membranes. At present, almost nothing is known about the intracellular biochemical pathways that are stimulated via the H_3-receptor. Several studies failed to show a coupling of H_3 receptors to intracellular cAMP levels;[10] a not completely understood, negative coupling to phospholipase C was shown in HGT-1 gastric tumor cells.[58] A coupling to N-type Ca^{2+}-channels, as shown for other presynaptic receptors, has been reported in functional studies with heart and duodenal preparations.[59, 60] The biochemical basis for this coupling is also, as yet, unknown.

Further Directions

Many new developments are awaited, particularly in the field of the H_3 receptor where both the primary receptor structure and the signal transduction pathway(s) are, as yet, unknown. However, new developments are expected in the next five years. For the H_1 and H_2 receptors, availability of the cDNAs will provide new insights on structure-function relationships of the receptor protein, receptor regulation, and gene expression, in the years to come.

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Histaminergics Available from Tocris

H_1 Receptor

Agonists

0646	HTMT	H_1 agonist

Antagonists

0784	Ketotifen	H_1 antagonist
0660	Mepyramine	Standard selective H_1 antagonist
0587	2-[4-(2-Methylethyl)phenyl]-3-[3-(N,N-dimethylamino)propyl]-1,3-thiazolidin-4-one	H_1 antagonist
0662	*trans*-Triprolidine	Standard H_1 antagonist, highly potent

H_2 Receptor

Agonists

0668	Amthamine	Highly selective standard H_2 agonist
0506	Dimaprit	Standard H_2 selective agonist

Antagonists

0902	Cimetidine	H_2 antagonist, I_1 agonist
0833	ICI-162,846	Potent H_2 antagonist, active *in vivo*
0826	Tiotidine	Potent, selective H_2 antagonist
1070	Zolantidine	Potent, centrally active H_2 antagonist

H_3 Receptor

Agonists

0729	Imetit	Standard selective H_3 agonist
0932	Immepip	Standard H_3 agonist
0573	N$^{\alpha}$-Methylhistamine	Non-selective H_3 agonist
0569	R(-)-α-Methylhistamine	Potent and selective standard H_3 agonist
0572	S(+)-α-Methylhistamine	H_3 agonist, less active enantiomer

Antagonists

0752	Clobenpropit	Highly potent, selective H_3 antagonist
0779	Iodophenpropit	Very potent and selective standard H_3 antagonist
0644	Thioperamide	H_3 antagonist, active *in vivo*

Histaminergics - Other

0743	DPPE	Inhibitor of histamine binding at the intracellular binding site
0512	SKF 91488	Histamine N-methyl transferase inhibitor

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