Histamine Receptors and Their Ligands

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Summary

Histamine, a biogenic amine, mediates multiple physiological effects through binding to its receptors, i.e., H_1, H_2, H_3, and H_4 receptors. Currently, the histamine receptors have taken attention as important targets for the treatment of several diseases and disorders. In this article, a short review about histamine, histamine receptors, and histamine receptor ligands is described in the state of art in molecular biology, pharmacology, and medicinal chemistry.

Introduction

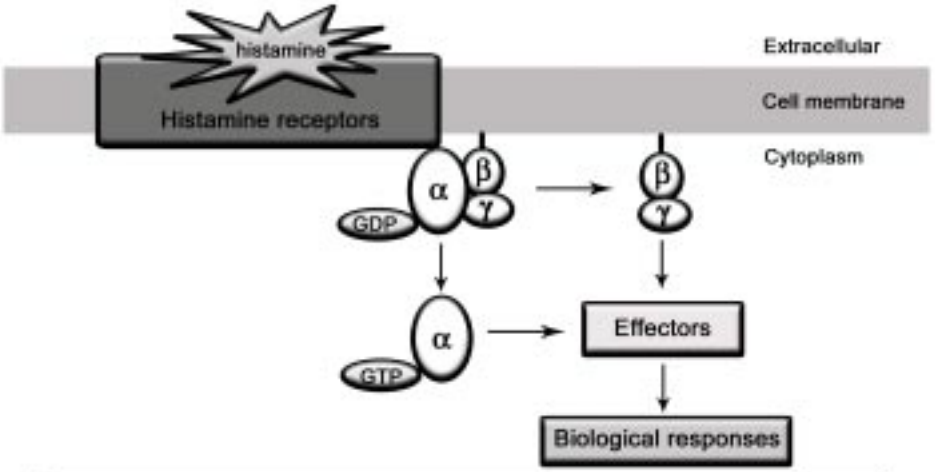
Histamine, a biogenic amine, was first identified as an autocoid having potent vasoactive properties (Ring, 1979). Subsequently, it was recognized for its multiple regulatory activities in the immune systems. Histamine is synthesized and stored in cytoplasmic granules within mast cells and basophils where it is released massively in response to various immunological or non-immunological stimulations (Goldstein and Halperin, 1977; Leid, 1979). The list of activities ascribed to histamine has steadily grown to include activities in inflammation, gastric acid secretion and neurotransmission. In the central nervous system (CNS), the amine is synthesized in a restricted population of neurons located in the tuberomammillary nucleus of the posterior hypothalamus. These neurons project diffusely to most cerebral areas and have been implicated in various functions of the mammalian brain;e.g., sleep/wakefulness, hormonal secretion (Waldman et al., 1977), cardiovascular control (Stasiewicz and Gabryelewicz, 1979), etc.

The biogenic amine is synthesized by decarboxylation of *L*-histidine using the pyridoxal-5'-phosphate-dependent *L*-histidine decarboxylase enzyme (HDC) via a histidine-PLP Schiff base intermediate (Finch and Hicks, 1976). Once released from the cytoplasmic granule, the histamine level is controlled by two major metabolic pathways, i.e., histamine-*N*-methyl transferase and diamine oxidase. Histamine is methylated at the N^{τ} imidazole by histamine-*N*-methyltransferase using S-adenosyl-*L*-methionine as cofactor. The methylhistamine produced is a substrate for monoamine oxidase-B and diamine oxidase. The aldehyde intermediate is further oxidized by aldehyde dehydrogenase to methylimidazole acetic acid. In the oxidative pathway, histamine is converted to imidazole acetaldehyde by diamine oxidase, and is then rapidly converted by aldehyde dehydrogenase to imidazole-4-acetic acid (Yatsunami et al., 1994). Only small amounts (2-3%) of the histamine released is excreted unchanged.

Histamine receptors and their isoforms

Using molecular cloning techniques, numerous G-protein-coupled receptors (GPCRs) have been identified. Like other aminergic receptors, i.e., serotonin, dopamine, muscarinic, and adrenergic receptor, the histamine receptors are classified as heptahelical G-protein-coupled receptors, and in particular categorized to the class "A" family (rhodopsin/ β_2-adrenergic receptor-like). The multiple biological activities of histamine were recently attributed to four histamine receptors (H_1, H_2, H_3 and H_4) transducing extracellular signals through different G-proteins; G_q for H_1, G_s for H_2, $G_{i/o}$ for H_3 and H_4 receptors (Figure 1). Phylogenetic analysis of the genes encoding human GPCRs within amine transmitter systems (Figure 2) indicates that the histamine H_3 and H_4 receptors are not closely related to the histamine H_1 and H_2 receptors, but

share a high homology to each other (35% overall homology and 58% homology in the transmembrane regions) (Abe et al., 1993).



Histamine receptors	G-proteins	Effectors
H1	Gαq	PLC, Ca^{2+}, NOS, cGMP, PLA2
H2	Gαs	cAMP, PLC, Ca^{2+}, c-fos
H3	Gαi and GTP-dependent mechanisms	inhibition of cAMP accumulation, Ca^{2+}, MAPK
H4	Gαi	inhibition of cAMP accumulation, MAPK

Figure 1 Structural characteristics of histamine receptors and their main effector molecules

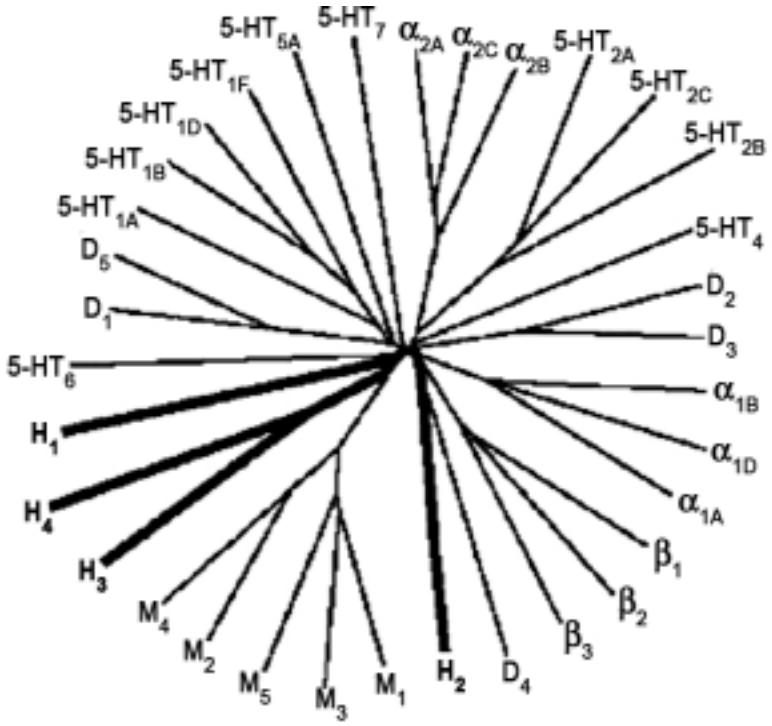


Figure 2 Phylogenetic tree shows the degree of homology between members of the GPCRs family of amine transmitter systems (modified from Stark et al., 2003)

With the polymerase chain reaction (PCR) and cloning techniques which are nowadays available, several subtypes and isoforms of the aminergic receptors have been discovered. Unlike the histamine H_1 and H_2 receptors, several isoforms of the histamine H_3 receptor have been identified for human (Stark et al., 2003), rat (Wellendorph et al., 2002), and guinea pig (Morisset et al., 2001). The alignment of the amino acid sequences of the six human, five rat and two guinea pig receptor isoforms is described. Among the human H_3 receptor variants, Coge and colleagues described that although the $H_{3(445aa)}$ and $H_{3(\Delta i3,365aa)}$ variants (an 80 amino acid deletion within the third intracellular loop of the protein) displayed a high affinity for a series of known H_3 agonists, the $H_{3(\Delta i3,365aa)}$ variant could be biologically inactive because agonist stimulation of this variant neither modified adenylyl cyclase activity nor induced intracellular Ca^{2+} mobilization (Tardivel-Lacombe et al., 2000). These results are in contrast to a recent study by Wellendorph and colleagues, using the Receptor Selection and Amplification Technology (R-SAT) assay to show activation of $H_{3(\Delta i3,365aa)}$ the variant by histamine H_3 agonist, i.e., histamine, (*R*)-α-methylhistamine, immepip, or imetit (Table 1). In this assay 3-20 fold increased functional agonist potencies (pEC_{50}) relative to the $H_{3(445aa)}$ variant was observed (Coge et al., 2001). The latter results, moreover, are consistent with those reported in the rat H_3 receptor where shifts in functional potencies for agonists were observed for the rat H_3 receptor isoforms that have analogous deletions within their third intracellular loop (Table 1). Regarding the earlier reports on structure-function relationships of G-protein coupled receptors, the third intracellular (i3) loop of the 7TM receptors is a major determinant of G-protein coupling for receptors but only the N- and C-terminal regions of the i3 (Ni3 and Ci3 respectively) are recently established as motifs required for the interaction with the G-protein (Figure 3). Whereas, the central portion of the i3 loop can be deleted without impairing coupling to G-protein. Using random saturation mutagenesis described by Burstein and colleagues, only a few amino acid residues at Ni3 and Ci3 regions are shown to involve the coupling to G-proteins for the muscarinic receptors (Spalding et al., 1995, Burstein et al., 1996). The studies on muscarinic receptor indeed support the observed activity upon activation of the $H_{3(\Delta i3,365aa)}$ variant in the Wellendorph study, whereas the loss of the functional activity in the Coge study remains unexplainable.

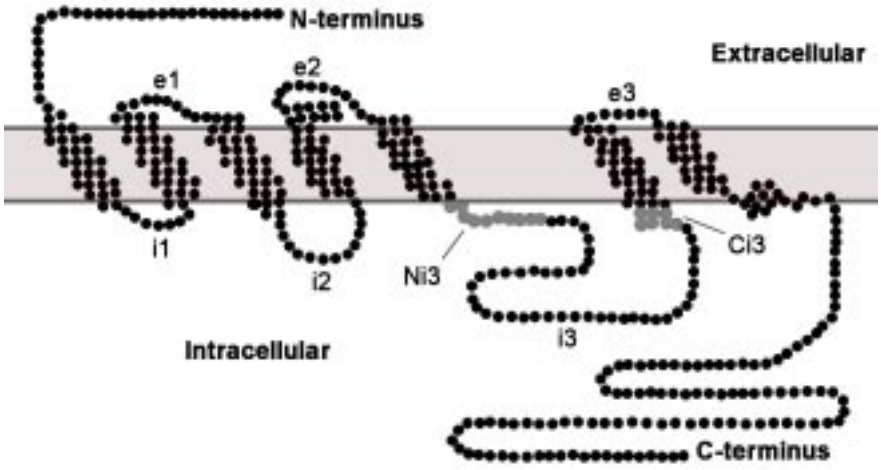


Figure 3 The molecular G-protein-coupled receptor model depicts N- and C-terminal regions of the third intracellular loop (Ni3 and Ci3 respectively) where G-proteins interact

Table 1 Affinities (pK_i) and functional activities (pEC_{50}) of various H_3 agonists for the different human and rat H_3 receptor isoforms

compound	Human H_3 receptor isoforms				Rat H_3 receptor isoforms					
	$H_{3(445aa)}$		$H_{3(\Delta i3,365aa)}$		$H_{3(445aa)}$		$H_{3(\Delta i3,413aa)}$		$H_{3(\Delta i3,397aa)}$	
	pK_i[a]	pEC_{50}[a,b]	pK_i[a]	pEC_{50}[b]	pK_i[c]	pEC_{50}	pK_i[c]	pEC_{50}	pK_i[c]	pEC_{50}[c]
histamine	8.2	7.5, 6.3	8.3	7.5	5.7	7.0[d]	6.2	6.8[d]	6.3	-
(*R*)-α-methylhistamine	8.7	8.6, 7.0	8.8	8.3	6.4	8.5[c]	6.9	9.1[c]	7.1	9.0
immepip	9.6	9.3, 8.1	9.7	8.8	7.5	9.4[c]	8.0	9.7[c]	8.0	9.8
imetit	9.4	8.8, 7.7	9.7	8.2	-	8.3[d]	-	9.4[d]	-	-

Note: [a]The pK_i and pEC_{50} values were determined using the [^{35}S]GTP[S] binding assay (coge et al., 2001).
[b]The pEC_{50} values were determined using the Receptor Selection and Amplification Technology (R-SAT) assay (Wellendorph et al. 2002).
[c]The pK_i and pEC_{50} values were determined by [^{125}I]IPP binding studies and the inhibition of forskolin-induced cAMP production respectively (Morisset et al., 2001).
[d]The pEC_{50} values were determined from A-23187-evoked [^{3}H] arachidonic acid release (Tardive-Lacombe et al., 2000).

Constitutive activity of G-protein-coupled receptors

The current most widely accepted model for GPCR activation is the extended ternary complex model (simply represented as a two states model shown in Figure 4) (Gether, 2000). In this model, the receptor exists in an equilibrium between an inactive conformation (R) and an active conformation (R*). In the absence of agonist, the inactive (R) and active (R*) states are believed to be in equilibrium since the energy barrier between R and R* state is sufficiently low enough to allow a certain fraction of the receptors spontaneously to assume the R* state. This equilibrium between the two states, moreover, implies that at any time a certain fraction of receptors may adopt a constitutively active state. The concept of constitutive activity has profoundly modified the understanding of GPCRs and revealed a full spectrum of activities ranging from full and partial agonism through 'silent' activity (neutral antagonism) to partial and full inverse agonism. Agonists are predicted to bind and stabilize the receptor conformation at the R* state or to shift the equilibrium and increase the proportion of the receptor in R* state. Conversely, inverse agonists are predicted to stabilize the inactive R state, shifting the equilibrium away from R* state. Neutral antagonists are defined as compounds that bind with equal affinity to both the R and R* states and thus cause no change in the equilibrium (Seifert & Wenzel-Seifert, 2002).

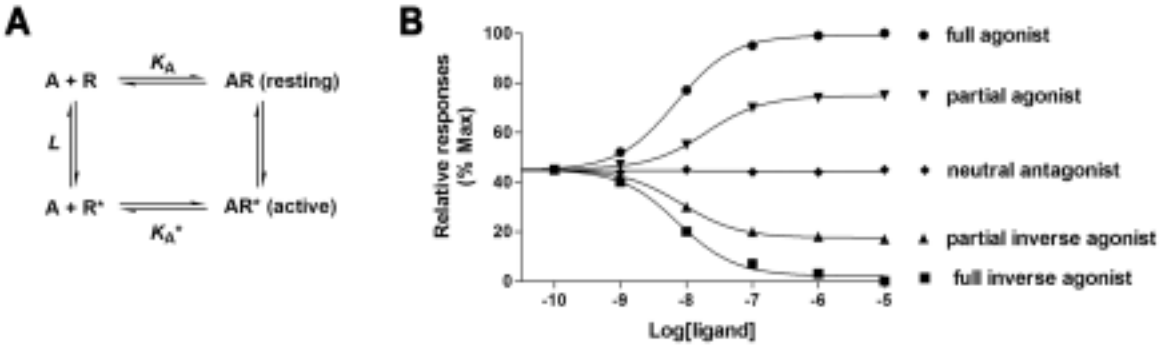


Figure 4 The GPCRs exist in two states, R (inactive) and R* (active). In the absence of agonist (A) the distribution of the two states is governed by the equilibrium constant *L*. The agonist has affinities for the two states governed by the dissociation equilibrium constant, K_A and K_A*. (B) R- to R* isomerization in GPCRs occurs, to a different extent, in the absence of agonist and is referred to as constitutive activity. The basal G-protein and effector activity are increased and decreased in the presence of agonist and inverse agonist respectively, whereas the basal level is not affected by neutral antagonist (antagonist).

As discussed before, some G-protein-coupled receptors have been studied and shown to display constitutive activity. In several studies, moreover, indicated that the constitutive activity can be detected in the system where the recombinant receptors expressed at high density or in the mutated receptors. It has therefore been argued whether the constitutive activity occurs in animals expressing normal levels of receptor protein. Studies on the histamine H_3 receptor, however, indicated the occurrence of constitutive activity both in cells stably expressing the histamine H_3 receptor and in vivo (rat brain) systems. Wieland and colleagues determined affinity and functional activity of ligands including impentamine and *N*-substituted impentamine analogues, at SK-N-MC cells stably expressing the human or rat recombinant histamine H_3 receptor (Wieland et al., 2001). In this series of ligands, substitution on the impentamine side chain nitrogen with various substituents resulted in different pharmacological responses (not significantly different in affinity, Figure 5). The results led to classify the activities of ligands ranging from full agonism, neutral antagonism to full inverse agonism. In a study in the rat brain by Morisset and colleagues, proxyfan was identified as a neutral antagonist at the histamine H_3 receptor. Proxyfan, which itself does not affect the normal basal level of histamine in rat brain, inhibits the responses mediated by histamine H_3 receptor agonist (imetit) and inverse agonist (FUB465, chemical structure is shown in Figure 8) (Morisset et al., 2000). The discovery of neutral antagonists at the histamine H_3 receptor both in vitro and in vivo studies in fact reflects the occurrence of constitutive activity of the histamine H_3 receptor.

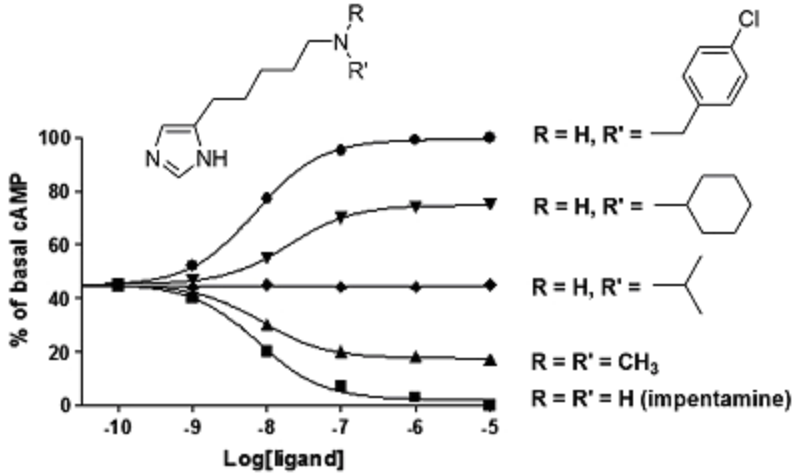


Figure 5 Modulation of forskolin induced cAMP production in SK-*N*-MC cell expressing the human H_3 receptor by impentamine and its derivatives

Distribution of histamine receptors and therapeutic potential of histaminergic ligands

The study of the distribution of histamine receptors in different tissues has been greatly aided by the development of selective radioligands and Northern blot analysis. [^{3}H]mepyramine has been used successfully to detect H_1 receptors in a wide variety of tissues (Carswell and Nahorski, 1982). In the mammalian brain, activation of the H_1 receptor causes inhibition of hyperpolarization and firing in hippocampus neurons and an apamine-sensitive outward current in olfactory bulb interneurons (Chang et al., 1980). However, many other neurons are excited by H_1 receptor activation through a block of potassium conductance. In vascular endothelial cells, stimulation of the H_1 receptor leads to several cellular responses including changes in vascular permeability as result of endothelial cell contraction, synthesis of prostacyclin and platelet-activating factor, and release of nitric oxide (Gruetter et al., 1994; Sharif et al., 1998). In the left atria, histamine produces negative inotropic effects (Levi et al., 1975).

So called antihistamines, histamine H_1 receptor antagonists, used clinically for treatment of allergy are mainly classified into two categories, i.e., classical (sedative) and non-sedative antihistamine. Some compounds, for example, promethazine, (+)-chloropheniramine and triprolidine can readily cross the blood brain barrier, thus causing sedative effect through the blockade of H_1 receptor (Nicholson et al., 1991). Whereas several other histamine H_1 blockers including fexofenadine, loratadine, and desloratadine (Figure 6), which penetrate poorly into the brain devoid the central depressant effects (Rose et al., 1982; Mann et al., 1989).

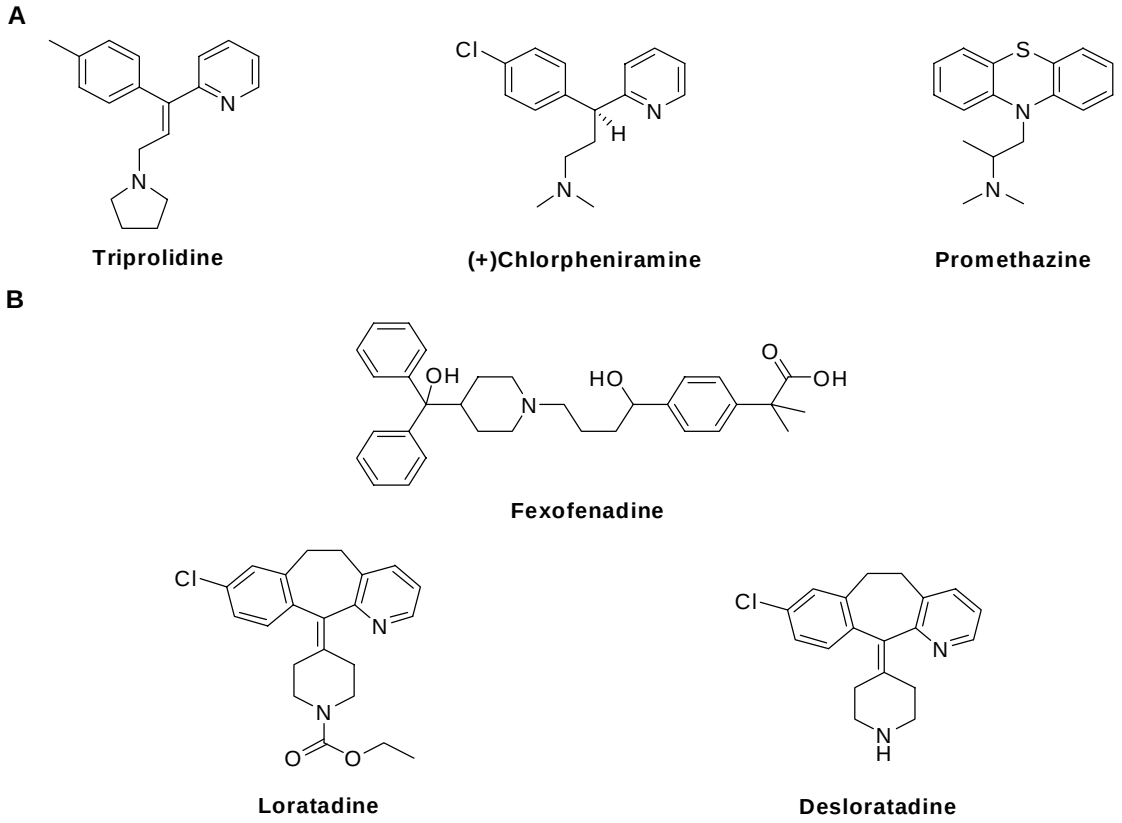


Figure 6 Chemical structures of some histamine H_1 receptor antagonists; (A) classical antihistamines and (B) non-sedative antihistamines

The discovery of [^{125}I]iodoaminopotentidine, a highly selective potent H_2 radioligand, allowed to identify the expression of the histamine H_2 receptor. In human brain, the H_2 receptor is widely distributed in the basal ganglia, hippocampus, amydala and cerebral cortex. Low expression of the H_2 receptor has been observed in cerebellum and hypothalamus (Ruat et al., 1990; Honrubia et al., 2000). Functional studies with the H_2 receptor ligands in different tissues, moreover, demonstrated the distribution of the receptor in brain, gastric cells and cardiac tissue (Dousa and Code, 1974; Nahorski et al., 1974; McNeill et al., 1980). Activation of the H_2 receptor provides a potent effect on gastric acid secretion and mediates in the heart positive chronotropic and inotropic effects on the left atrial or ventricular tissues. Activation of the H_2 receptor causes relaxation of smooth muscles in uterus and blood vessels (Hagen and Paegelow, 1979; Harvey and Owen, 1979). Several histamine H_2 receptor antagonists (neutral antagonists or inverse agonists), for instance cimetidine (Burland et al., 1975), nizatidine (Callaghan et al., 1987), ranitidine (Bradshaw et al., 1979), and famotidine (Takagi et al., 1982), are used clinically for the treatment of peptic ulcer (Figure 7).

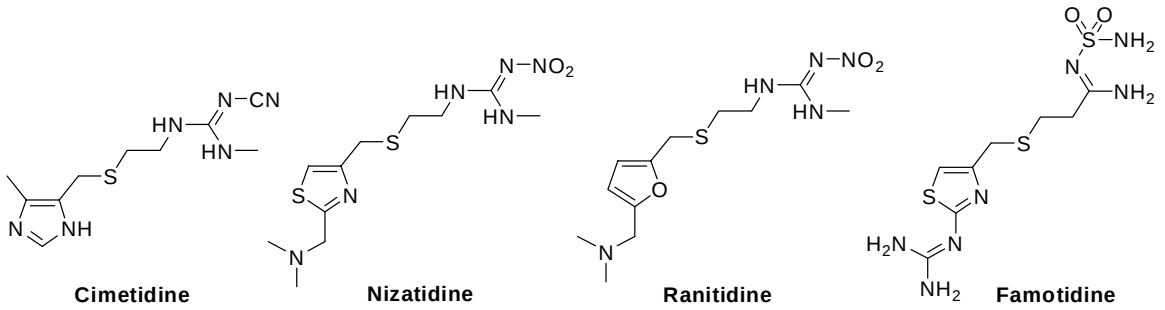


Figure 7 Chemical structures of some histamine H_2 receptor ligands

The histamine H_3 receptor, firstly reported in 1983, was primarily identified as an autoreceptor modulating the release and synthesis of histamine in human and rat cerebral cortex striatum and hippocampus (Arrang et al., 1983). It was subsequently identified to act as a heteroreceptor, regulating the release of several neurotransmitters, i.e., serotonin, noradrenaline, acetylcholine and dopamine in mammalian brain (Schwartz et al., 1990). Using cloning techniques, the histamine H_3 receptor gene was successfully cloned from various species. Although Northern blot analysis revealed that the histamine H_3 receptor mRNA is mainly expressed in the brain (Lovenberg et al., 1999), inhibitory effects of the H_3 receptor activation on neurotransmission have also been identified in the periphery (Ohkubo et al., 1994). There is also evidence that activation of the histamine H_3 receptor can inhibit the release of neurotransmitters from nonadrenergic-noncholinergic nerves in guinea pig bronchioles and ileum (Trzeciakowski, 1987; Burgaud and Oudart, 1993). Activation of the H_3 receptor inhibits the release of proinflammatory tachykinins and calcitonin-gene-related peptide (CGRP) from sensory C-fibres in various tissues, indirectly depresses mast cell activity and leads to peripheral antinociceptive activity (Ichinose et al., 1990; Rouleau et al., 1997). Moreover, the inhibitory effect of the H_3 activation on the release of serotonin (5-HT) from porcine enterochromaffin cells of small intestine was also reported (Schworer et al., 1994). Subsequently, it has been shown that the H_3 receptor present on gastric mast cells involves in the gastric acid secretion and histamine release. Activation of the H_3 receptor has been shown to inhibit gastric acid secretion in conscious cats and dogs, whereas an autoregulation of histamine synthesis by histamine H_3 receptor has been reported in the isolated rabbit fundic mucosal cells (Coruzzi et al., 1991; Bado et al., 1995). The activation of the histamine H_3 receptor also reduces myocardial exocytotic and carrier-mediated noradrenaline release (Levi and Smith, 2000). Thus, histamine H_3 receptor agonists have been proposed for the treatment of inflammation (Rouleau et al., 1997) , gastric acid related disease (Soldani et al., 1999), and myocardial ischemia (Hatta et al., 1997). The histamine H_3 receptor antagonists are especially expected to be useful for the treatment of several CNS disorders including attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease, epilepsy, schizophrenia, and obesity (Morisset et al., 1996; Leurs et al., 1998; Vohora et al., 2001).

Before the discovery of a novel histamine (H_4) receptor, several ligands have been identified as potent and highly selective H_3 receptor agonists including (R)-α-methylhistamine, imetit, and immepip (Figure 8). However, these ligands also exhibit high affinity at the H_4 receptor. Many ligands have been developed using the potent H_3 agonist immepip as prototype. Replacement of the piperidine ring of immepip with a pyridine ring led to the discovery of immethridine which exhibits a high affinity at the H_3 receptor with a 300-fold selectivity over its closely related H_4 receptor (Kitbunnadaj et al., 2004). Recently, Kitbunnadaj and colleagues identified a potent and highly selective H_3 agonist, methimepip, possessing a nanomolar affinity at the H_3 receptor with

a 2000-fold selectivity over the H_4 receptor and more than a 10000-fold selectivity over the H_1 and H_2 receptors. For the histamine H_3 antagonists, several imidazole-derived derivatives such as thioureas (thioperamide) (Arrang et al., 1988), isothioureas (clobenpropit) (Kathmann et al., 1993), ethers (iodoproxyfan) (Schunack and Stark, 1994), hydrocarbons (GT-2331, Perceptin®) (Tedford et al., 1998) have been described previously (Figure 8). Many compounds, however, are not selective to the H_3 receptor, for instance, clobenpropit and thioperamide which also show high affinity at the H_4 receptor. Currently, a novel non-imidazole compound, A-317920, was identified with improved selectivity and high affinity for the H_3 receptor (Fox et al., 2003).

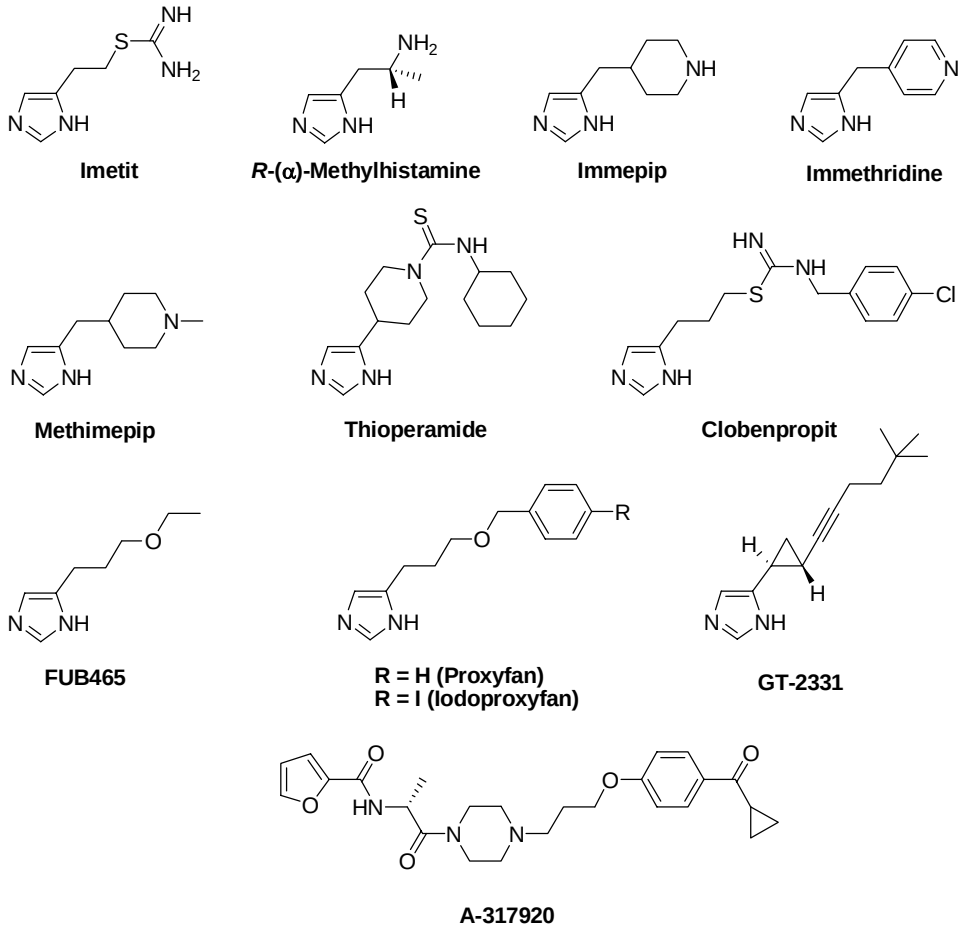
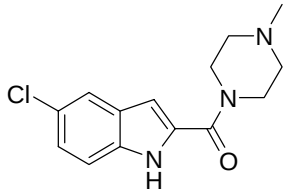


Figure 8 Chemical structures of some histamine H_3 receptor ligands

In 2000, Oda and colleagues identified a novel type of histamine receptor which has a relatively high homology with the histamine H_3 receptor, compared to the histamine H_1 and H_2 receptors. The new receptor is currently known as the histamine H_4 receptor. Tissue distribution of the histamine H_4 receptor analyzed by MTN (Multiple Tissue Northern) blot and PCR techniques revealed that the histamine H_4 receptor is mainly expressed on eosinophils and mast cells, and with detectable levels in the thymus, small intestine, spleen and colon (Oda et al., 2000). Thus the receptor is expected to play a role in inflammatory processes. A recent study by Hofstra and colleagues showed that the histamine induced chemotaxis of mouse mast cells is blocked by thioperamide which is a dual histamine H_3/H_4 receptor antagonist. This inhibitory effect of thioperamide, however, is not mediated through the histamine H_3 receptor since Northern blot analysis showed that the histamine H_4 (but not H_3) receptor expresses on the mast cells (Hofstra et al., 2003). Some studies suggest that activation of the H_4 receptor induces the release of bioactive

interleukin-16 from human $CD8^+$ T cells and produces an increase in cytosolic calcium in eosinophils (Gantner et al., 2002). Therefore, histamine H_4 receptor antagonists which inhibit the aforementioned responses are targeted as anti-inflammatory agents. In 2003, the first potent and highly selective H_4 receptor antagonist (JNJ-7777120) is identified (Figure 9). The compound blocks histamine-induced chemotaxis and calcium influx in mouse bone marrow-derived mast cells and histamine-induced migration of tracheal mast cells from the connective tissue toward the epithelium in mice (Thurmond et al., 2004).



JNJ-7777120

Figure 9 Chemical structure of JNJ-7777120

Conclusion

To date, the roles of histamine have been described as autocoid and important neurotransmitter. It provides distinct physiological responses through the activation of different histamine receptor subtypes, i.e., H_1, H_2, H_3, and H_4 receptor. Ligands antagonizing either the H_1, H_2, H_3 or H_4 receptor are expected as therapeutic agents; the H_1 and H_2 antagonists have been used clinically for the treatment of allergy and gastric ulcer, respectively, whereas some H_3 and H_4 receptor antagonists are currently in the clinical trials for the treatment of CNS disorders and inflammation, respectively. Unlike H_1, H_2 and H_4 receptor agonists which have not been used for the treatment of diseases and disorders, ligands activating through the H_3 receptor (H_3 agonists) have represented a new therapeutic frontier in myocardial ischemia. Thus, many pharmaceutical research groups have taken attention to the discovery of ligands selectively act at a certain subtype of histamine receptor in particular the H_3 and H_4 receptors which are recently identified.

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