Kirk-Othmer Encyclopedia of Chemical Technology.

HISTAMINE AND HISTAMINE ANTAGONISTS

The history of histamine [51-45-6], $C_5H_9N_3$ (1), and the development of antihistamines have been reviewed (1, 2). Histamine was the first to be characterized of a series of biogenic amines that are released in the inflammatory process (Fig. 1). As early as 1910, it was shown that histamine caused constriction of isolated guinea pig ileum and, subsequently, it was found that histamine induced a shock-like syndrome. In 1927 the presence of histamine in normal tissues was demonstrated. Attempts to reduce histamine manifestations led to the report, in 1933, that certain phenolic ethers inhibited histamine action (3). Toxicity precluded clinical use. In 1942 phenbenzamine [961-71-7] (Antergan), $C_{17}H_{22}N_2$, was the first antihistamine to be successfully used in humans (4).

In 1966, the name H_1 was proposed (5) for receptors blocked by the at that time known antihistamines. It was also speculated that the other actions of histamine were likely to be mediated by other histamine receptors. The existence of the H_2 receptor was accepted in 1972 (6) and the H_3 receptor was recognized in rat brain in 1983 (7). H_3 receptors in the brain appear to be involved in the feedback control of both histamine synthesis and release, whereas release of various other neurotransmitters, eg, serotinin (5-HT), dopamine, noradrenaline, and acetylcholine, is also modulated (8) (see Neuroregulators). H_3 receptor effects have also been demonstrated in various peripheral tissues and as of this writing H_3 agonists and antagonists are undergoing intensive study for therapeutic applications.

1. Histamine Synthesis, Metabolism, and Distribution

The synthesis and disposition of histamine is well described both in allergy textbooks (9, 10) and in review articles (11).

1.1. Synthesis

Histamine [51-45-6], 2-(4-imidazolyl)ethylamine (1) is formed by decarboxylation of histidine by the enzyme L-histidine decarboxylase (Fig. 1). Most histamine is stored preformed in cytoplasmic granules of mast cells and basophils. In humans mast cells are found in the loose connective tissue of all organs, especially around blood and lymphatic vessels and nerves. These cells are most abundant in the organs expressing allergic diseases: the skin, respiratory tract, and gastrointestinal tract.

1.2. Histamine Release

Antigen cross-linked immunoglobulin E (IgE) is the classic mast cell secretagogue in allergic diseases, but other physiologic mediators may also be involved, eg, opioids (qv) or neuropeptides. Basophil degranulation is caused by histamine-releasing factors, which are produced by most inflammatory cells, eg, neutrophils, platelets, and eosinophils. Several of the cytokines also cause basophil degranulation. Mast cells may also form a functional

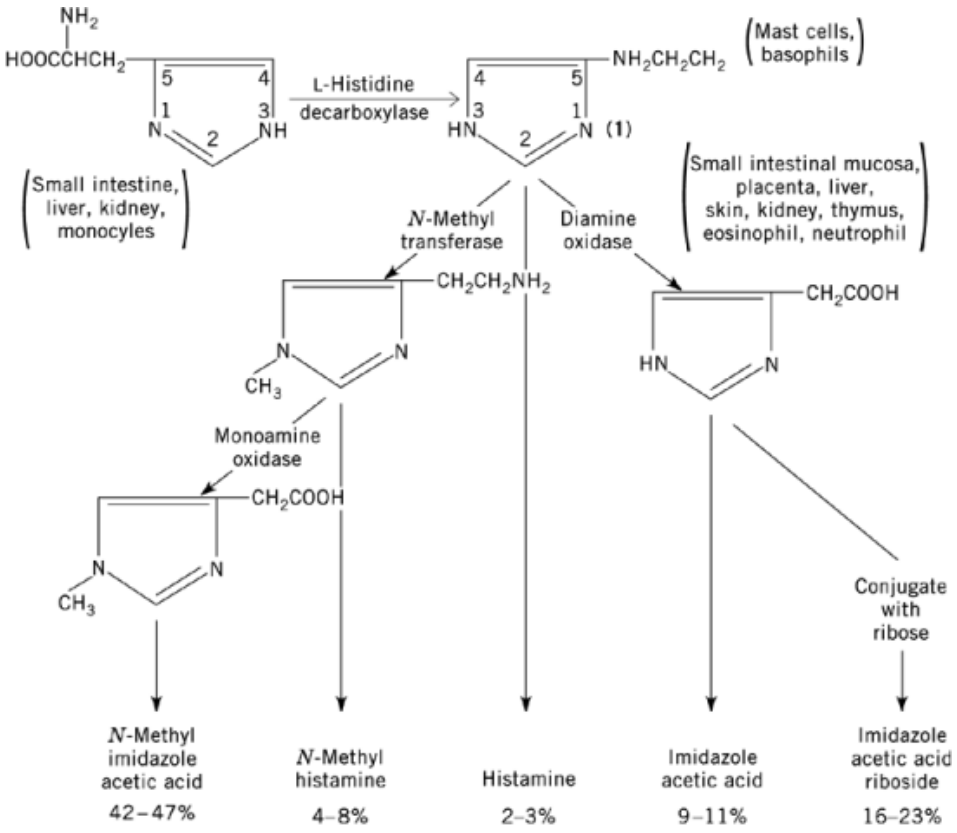


Fig. 1. Synthesis and metabolism of histamine (1) from histidine.

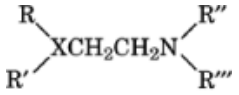
link between sensory nerve terminals and blood vessels, as these seem to be in close proximity to sensory nerve terminals. In addition, several sensory neuropeptides have histamine-releasing activity, suggesting a possible role of histamine in sensory nervous system functions. Thus histamine could play a special role in reinforcing the inflammatory response (see Immunotherapeutic agents).

1.3. Histamine in the Blood

After its release, histamine diffuses rapidly into the blood stream and surrounding tissues (12). Histamine appears in blood within 2.5 min after its release, peaks at 5 min, and returns to baseline levels by 15 to 30 min. In humans, the diurnal mean of plasma histamine levels is 0.13 ng/g. In urine, elevations of histamine or metabolites are more prolonged than plasma elevations. Consequently, abnormalities are more easily detected by urinary histamine assay. About one-half of the histamine in normal blood is in basophils, one-third in eosinophils, and one-seventh in neutrophils; the remainder is distributed among all the other blood components. Increases in blood histamine levels occur in several pathological conditions, but provide no positive evidence for the involvement of histamine in the pathogenesis of various diseases (13). In asthmatic patients blood histamine levels appear to be higher during asthmatic attacks but are close to normal during intermissions (see Antiasthmatic agents).

1.4. Metabolism

Metabolism of histamine occurs via two principal enzymatic pathways (Fig. 1). Most (50 to 70%) histamine is metabolized to *N*-methylhistamine by *N*-methyltransferase, and some is metabolized further by monoamine oxidase to *N*-methylimidazoleacetic acid and excreted in the urine. The remaining 30 to 40% of histamine is metabolized to imidazoleacetic acid by diamine oxidase, also called histaminase. Only 2 to 3% of histamine is excreted unchanged in the urine.



(2)

Table 1. Classical H_1 Antagonists

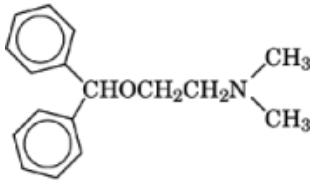
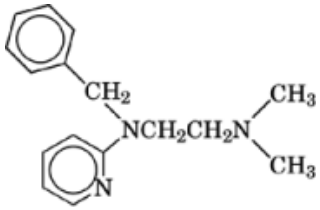
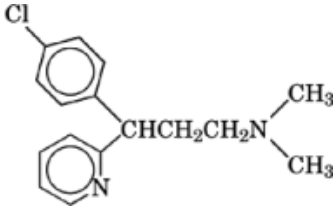
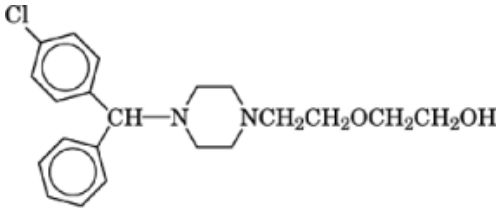
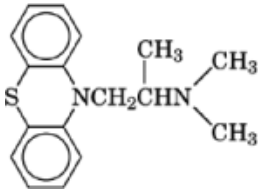
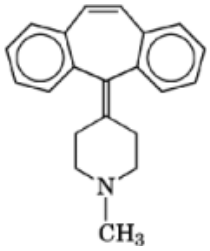
Compound	CAS Registry Number	Molecular formula	Structure
		Aminoalkylether	
diphenhydramine	[58 – 73 – 1]	$C_{17}H_{21}NO$	
		Ethylenediamine	
tripelennamine	[91 – 81 – 6]	$C_{16}H_{18}N_3$	
		Alkylamine	
chlorpheniramine	[132 – 22 – 9]	$C_{16}H_{19}ClN_2$	
		Piperazine	

Table 1. ***Continued***

Compound	CAS Registry Number	Molecular formula	Structure
hydroxyzine	[68 − 88 − 2]	$C_{21}H_{27}ClN_2O_2$	
		Phenothiazine	
promethazine	[60 − 87 − 7]	$C_{17}H_{20}N_2S$	
		Piperidine	
cyproheptadine	[129 − 03 − 3]	$C_{21}H_{21}N$	

1.5. Histamine in the Brain and the Histamine Neurone System

There is evidence that histamine functions as a neurotransmitter or a neuromodulator in the brain (14). In the mammalian brain, several thousand cell bodies are located in the posterior basal hypothalamus, comprising a functional unit, the tuberomamillary nucleus. The latter sends nerve fibers widely and unevenly to various regions from the olfactory bulb to the spinal cord. In the brain, histamine is related to functions such as the regulation of neuroendocrine and cardiovascular systems, thermoregulation, the circadian rhythm of sleep–wakefulness, behavior, vestibular function, cerebral vascular regulation, and antinociception and analgesia.

1.6. Histamine in the Cardiovascular System

It has been known for many years that histamine is present in sympathetic nerves and has a distribution within the heart that parallels that of norepinephrine (see Epinephrine and norepinephrine). A physiological role for cardiac histamine as a modulator of sympathetic responses is highly plausible (15). A pool of histamine

in rat heart located neither in mast cells nor in sympathetic nerves has been demonstrated. The turnover of this metabolically active pool of histamine appears to be maintained by normal sympathetic activity.

Table 2. Second-Generation H_1 Antagonists

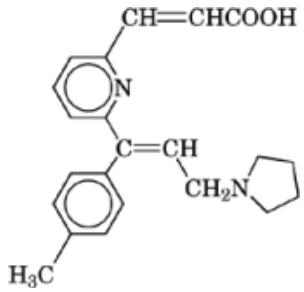
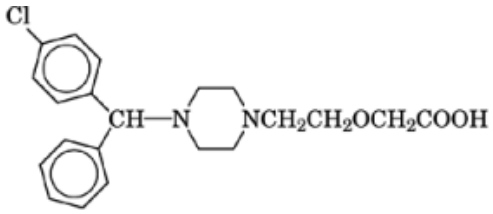
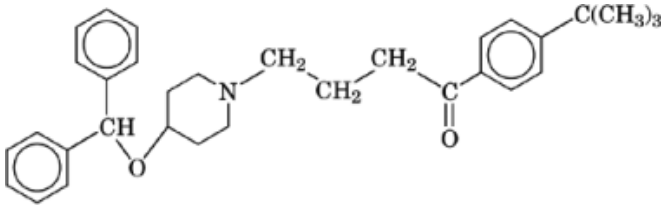
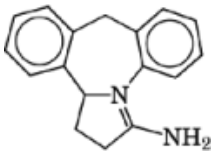
Compound	CAS Registry Number	Molecularformula	Structure	Structure number
			Classical structures	
acrivastine	[87848-99-5]	$C_{22}H_{24}N_2O_2$		**(3)**
cetirizine	[83881-51-0]	$C_{21}H_{25}ClN_2O_3$		**(4)**
ebastine	[90729-43-4]	$C_{32}H_{39}NO_2$		**(5)**
epinastine	[80012-43-7]	$C_{16}H_{15}N_3$		**(6)**

Table 2. ***Continued***

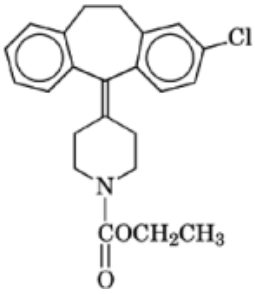
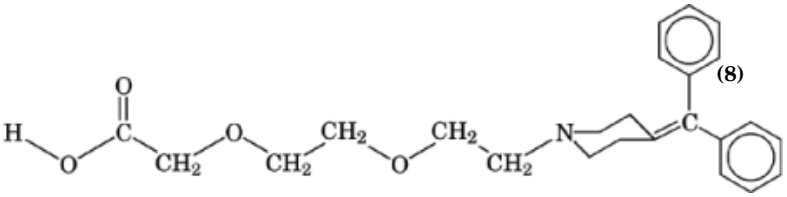
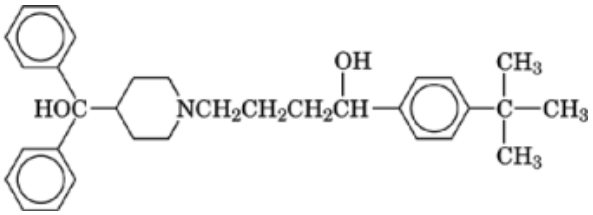
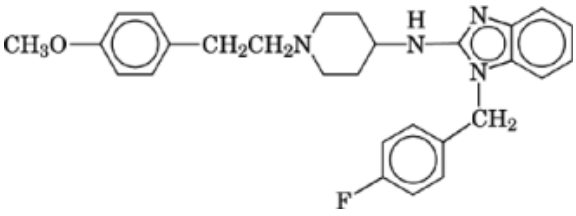
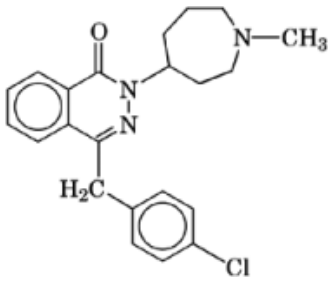
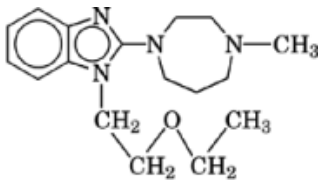
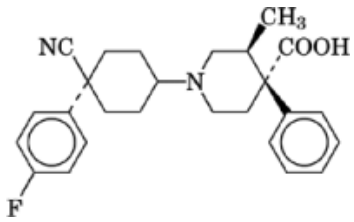
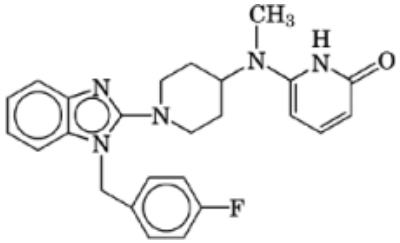
Compound	CAS Registry Number	Molecularformula	Structure	Structure number
loratadine	[79794-75-5]	$C_{22}H_{23}N_2O_2Cl$		**(7)**
pibaxizine	[82227-39-2]	$C_{24}H_{29}NO_4$		**(8)**
terfenadine	[50679-08-8]	$C_{32}H_{41}NO_2$		**(9)**
		Nonclassical structures		
astemizole	[68844-77-9]	$C_{28}H_{31}FN_4O$		**(10)**

Table 2. ***Continued***

Compound	CAS Registry Number	Molecularformula	Structure	Structure number
azelastine	[58581-89-8]	$C_{22}H_{24}ClN_3O$		**(11)**
emedastine	[87233-61-2]	$C_{17}H_{26}N_4O$		**(12)**
levocabastine	[79516-68-0]	$C_{26}H_{29}FN_2O_2$		**(13)**
mizolastine	[108612-45-9]	$C_{24}H_{25}FN_6O$		**(14)**

2. Histamine Receptors

The actions of histamine are mediated through at least three distinct receptors defined pharmacologically by the actions of the respective agonists and antagonists. Reviews have been published (16, 17).

2.1. The H_1 Receptor and Its Ligands

The H_1 receptor mediates most of the important histamine effects in allergic diseases (11). These include smooth muscle contraction, increased vascular permeability, pruritus, prostaglandin generation, decreased atrioventricular node conduction time with resultant tachycardia, activation of vagal reflexes, and increased cyclic guanosine monophosphate (cGMP) production. The mean density of cerebral H_1 receptors is about 100 fmol/mg membrane protein, in the same range as that of receptors of other neurotransmitters. In the human brain the highest density is found in the neocortex and various limbic structures.

2.1.1. H_1 Receptor Agonists

In the histamine molecule there are two principal structural elements: an imidazole moiety and an ethylamine side chain (16). Only the N^{π}-position is absolutely necessary for H_1 agonism. The imidazole ring can be replaced, eg, 2-pyridylethylamine, 2-thiazolylethylamine, or substituted at the 2-position. 2-Methylhistamine is often used as a selective H_1 agonist; however, larger substituents are not allowed unless a phenyl ring is used. 2-Phenylhistamine analogues appear to be very selective H_1 receptor agonists. In this series of compounds both full and partial agonists and even H_1 antagonists are encountered, representing useful tools for studies of pharmacology and structure—activity relationships. Methylation of the amine group is allowed, but this change does not lead to selective compounds.

2.1.2. H_1 Receptor Antagonists

The classical H_1 receptor antagonists are reversible, competitive, dose-dependent inhibitors of the action of histamine on H_1 receptors. Histamine H_1 antagonists are usually divided into two classes: the first-generation or classical H_1 antagonists and the second-generation H_1 antagonists. The main distinction between the first- and second-generation drugs is the absence of sedative and anticholinergic side effects in the latter.

2.1.2.1. Classical H_1 Receptor Antagonists. Since the initial discovery of an anti-histaminic compound in 1933, a very high number of potent compounds were synthesized. Several reviews are available (16, 18–20).

The classical histamine H_1 receptor antagonists are structurally very similar, all being substituted ethylamines (**2**). Table 1 presents a member of each structural subclass. Presumably, the ethylamine core is needed to accomplish nonfruitful binding to the high affinity conformation of the receptor. The other substituents modify the physical chemistry of the compounds. A disubstituted terminal amino group, often a dimethylamino group, is connected to an atom X via a short carbon chain. The chain can be saturated, unsaturated, branched, or part of a ring system, whereas X can be an oxygen, nitrogen, or carbon atom or a polyatomic group; X links the side chain to the aromatic region. This aromatic part generally contains two aromatic rings, eg, phenyl, thiophene, 2-pyridyl, which may eventually be fused to form tricyclic derivatives. Based on the type of X-linkage and the type of aromatic region, the classical H_1 receptor antagonists can be subdivided into six classes: aminoalkylethers, ethylenediamines, alkylamines, piperazines, phenothiaxines, and piperidines.

The prototype aminoalkylether or ethanolamine is diphenhydramine (Benadryl). Clemastine [15686-51-8], $C_{21}H_{26}ClNO$, differs from it in having one phenyl ring chlorinated, a methylated benzhydryl carbon, and a three-carbon amino side chain, partly incorporated into a pyrrolidinyl ring system. Setastine [64294-95-7], $C_{22}H_{28}ClNO$, which has been launched in Hungary, differs from clemastine only in the type of heterocyclic ring.

The prototype of a pure ethylenediamine is tripelennamine; antazoline [91-75-8], $C_{17}H_{19}N_3$, belongs to the same family of compounds. Several well-known alkylamines in addition to chlorpheniramine are known.

Dexchlorpheniramine maleate [2438-32-6] and triprolidine monohydrochloride monohydrate [6138-79-0], an alkenyl derivative, are two examples.

Replacement of the oxygen bridge atom of diphenhydramine by nitrogen and incorporation of the two nitrogens into a piperazine ring leads to cyclizines. Hydroxyzine is a well-known piperazine derivative. Cinnnarizine [298-57-7], $C_{26}H_{28}N_2$, and oxatomide [60607-34-3], $C_{27}H_{30}N_4O$, both structurally related to cyclizine [82-92-8], differ only by having respectively a cinnamyl or a propylbenzimidazolone *N*-substituent instead of a methyl group. Oxatomide also has mast cell stabilizing actions.

There are two types of tricyclic H_1 antagonists: the phenothiazine and piperidine derivatives. Promethazine is the prototype molecule of the phenothiazine derivatives. Mequitazine [29216-28-2], $C_{20}H_{22}N_2S$, a quinuclidinylmethyl derivative, is less sedative than promethazine. Cyproheptadine and pizotifen [5189-11-7], $C_{19}H_{21}NS{\cdot}C_4H_6O_5$, are piperidine derivatives. Though antihistamines, they are mainly used because of their antiserotonergic properties. Azatadine maleate [3978-86-7], $C_{20}H_{22}N_2$, is a pyridyl variant of cyproheptadine. The compound mianserin hydrochloride [21535-47-7], $C_{18}H_{21}ClN_2$, may structurally be regarded as a double-bridged analogue of phenbenzamine. Ketotifen [34580-14-8], $C_{19}H_{19}NOS$, is also a piperidine derivative; like oxatomide, it has mast cell stabilizing actions besides its antihistamine properties.

2.1.3. Second-Generation H_1 Receptor Antagonists

Because of undesirable side effects caused by classical H_1 receptor antagonists, drugs having enhanced clinical effectiveness and a reduced side-effect profile have been sought. The main progress has been in the development of antihistamines that, unlike the classical H_1 antagonists, do not cause sedation. Thus the term second-generation antihistamines usually refers to those nonsedating antihistamines. The reduced ability to penetrate the central nervous system (CNS) can generally be explained by physicochemical properties. Several reviews address these new antihistamines (16, 21, 22). Table 2 shows some of the second-generation H_1 antagonists.

Several antihistamines have been derived from classical structures that do not penetrate into the brain. Most of these compounds are modifications of the classical H_1 receptor antagonists. Terfenadine (**9**) was studied as part of a butyrophenone program for new antipsychotics (see Psychopharmacological agents). Whereas it was ineffective in the models used because it did not cross the blood brain barrier readily, terfenadine was then found to be an effective H_1 receptor antagonist having little or no central activity. Oxidative metabolization of hydroxyzine afforded the active metabolite cetirizine (**4**). Owing to the presence of a carboxy group, cetirizine has a reduced access to the CNS as compared to the parent compound. An analogue of cetirizine, pibaxizine (**8**) is being developed.

Modification of the classical H_1 antagonist azatadine also resulted in a potent nonsedating antihistamine, loratadine (**7**). *Ex vivo* binding studies in animals demonstrated a selectivity for occupancy of lung H_1 receptors compared with cerebral cortex H_1 receptors, which might partially explain the observed lack of significant CNS activity. Acrivastine (**3**) is closely related to the potent alkylamine H_1 receptor antagonist triprolidine.

Ebastine (**5**) is a more recent H_1 antagonist which structurally may be considered a hybrid between diphenylpyraline [147-20-6], $C_{19}H_{23}NO$ (**7**), a classical antihistamine, and terfenadine (**9**). Epinastine (**5**), structurally related to the antidepressant and sedative H_1 receptor antagonist mianserin [24219-97-4], $C_{18}H_{20}N_2$, has reduced CNS penetration probably because of its different physicochemical properties.

Some of the second-generation H_1 antagonists have nonclassical structures. The phthalazinone derivative azelastine (**11**) combines potent H_1 receptor antagonism with moderate to weak serotonergic, leukotriene C_4 and D_4, and platelet activating factor (PAF) receptor antagonism. Besides an oral formulation, a nasal spray has also been developed. A somewhat unusual side effect of azelastine is taste alteration. Astemizole (**10**), a benzimidazole derivative, is a potent H_1 receptor antagonist having moderate serotonin- and α1-adrenergic blocking activity. The most striking property is its extremely slow rate of dissociation from H_1 receptors *in vitro.* A unique feature of astemizole is the presence of a guanidino function, although incorporated in a benzimidazole

ring system. This property may contribute to the compound's failure to penetrate the CNS. Other benzimidazole derivatives being developed include emedastine (**12**) and mizolastine (**14**).

Astemizole (**10**) has further been modified into a series of 4-phenylcyclohexylamine compounds, resulting in the synthesis of cabastine, for example. Cabastine is a highly active compound and its geometric isomers are also active, demonstrating the stereoselectivity of histamine H_1 receptors toward chiral ligands. The 3 *S,* 4 *R*-levo antipode of cabastine was the most active, and therefore this isomer, levocabastine (**13**), has been chosen for further development. Because of high potency, levocabastine has been developed for topical application such as eye drops and nasal spray.

Compounds have also been described (23) in which H_1 receptor antagonism is combined with histamine H_2 receptor agonism. These are primarily derivatives of the potent H_2 receptor agonist impromidine. Also, compounds having other dual activity are being developed, eg, Schering 37370, an antagonist of PAF and H_1 receptors and AL-3264 (Dainippon), a 5-lipoxygenase inhibitor with H_1 blocking activity.

2.2. The H_2 Receptor and Its Ligands

The discovery of H_2 receptors and antagonists occurred in 1972. This topic, including therapeutic implications, is considered in more detail elsewhere (see Gastrointestinal agents).

2.2.1. H_2 Receptors

The H_2 receptor mediates effects, through an increase in cyclic adenosine monophosphate (cAMP), such as gastric acid secretion; relaxation of airway smooth muscle and of pulmonary vessels; increased lower airway mucus secretion; esophageal contraction; inhibition of basophil, but not mast cell histamine release; inhibition of neutrophil activation; and induction of suppressor T cells. There is no evidence that the H_2 receptor causes significant modulation of lung function in the healthy human subject or in the asthmatic, except for some weak relaxing effect (24). In the brain, the H_2 receptors are distributed widely and mainly in association with neurones.

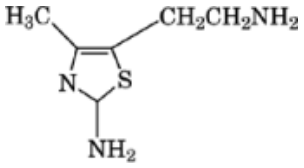
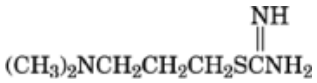
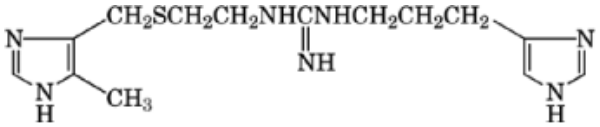
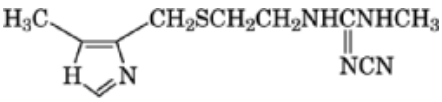
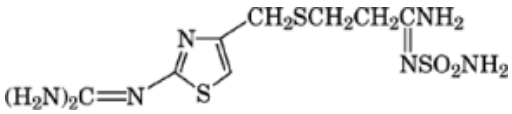
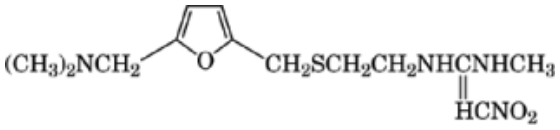
Combined H_1/H_2 receptor stimulation by histamine is responsible for vasodilation-related symptoms, such as hypotension, flushing, and headache, as well as for tachycardia stimulated indirectly through vasodilation and catecholamine secretion.

2.2.2. Histamine H_2 Receptor Agonists

Extended reviews on histamine H_2-active compounds have been published (16, 25). Structural requirements of histamine as an H_2 agonist are considered to be the protonated side-chain nitrogen atom and the ability of the imidazole amidine system to undergo a tautomeric shift. 4-Methylhistamine is often used as a selective H_2 agonist. Larger substituents are not allowed. Methylation of the amine group is allowed but leads to nonselective analogues.

H_2 agonists are divided in three chemical classes, ie, analogues of histamine (1), dimaprit (**16**), and impromidine (**17**) (Table 3). In histamine analogues, substitution of the imidazole ring results in many cases in a sharp decrease in H_2 agonistic activity. Dimaprit, a highly selective H_2 agonist, is a simple nonaromatic compound. The optimal chain length in dimaprit for H_2 agonistic activity corresponds to three CH_2 groups, which is contrary to histamine having two CH_2 groups as optimal chain length. Comparison of the structures of histamine and dimaprit have also led to the development of a new class of H_2 agonists (26, 27). The thiazole amthamine (**15**) appears to be a selective and rather potent H_2 agonist. It is remarkable in that in this compound the tautomeric shift, suggested to be essential for H_2 receptor activation, is impossible. Impromidine, a highly potent H_2 agonist, is a substituted guanidine. It is much more potent than histamine, which appears to be the result of an increased affinity of the compound for H_2 receptors rather than an increased efficacy. Other studies have shown that impromidine is an antagonist of both H_1 and H_3 receptors.

Table 3. H_2 Agonists and Antagonists

Compound	CAS Registry Number	Molecular formula	Structure	Structure number
			H_2 agonists	
amthamine	[142437 – 67 – 0]	$C_6H_{11}N_3S$		(**15**)
dimaprit	[65119 – 89 – 3]	$C_{16}H_{15}N_3S$		(**16**)
impromidine	[55273 – 05 – 7]	$C_{14}H_{23}NS$		(**17**)
			H_2 antagonists	
cimetidine	[51484 – 61 – 9]	$C_{10}H_{16}N_6S$		(**18**)
famotidine	[76824 – 35 – 6]	$C_8H_{15}N_7O_2S_3$		(**19**)
ranitidine	[66357 – 35 – 5]	$C_{13}H_{22}N_4O_3S$		(**20**)

From a therapeutic point of view, selective H_2 agonists may become useful in the treatment of heart failure and catecholamine-insensitive cardiomyopathy, but only if compounds become available that do not stimulate gastric acid secretion or cause other unforeseen problems.

2.2.3. Histamine H_2 Receptor Antagonists

In 1972 a new class of histamine antagonists was described that was capable of antagonizing histamine-induced gastric acid secretion (6). The H_2 antagonists are divided into five structural classes, some of which are shown in Table 3. A more complete review can be found in Reference 25.

The H_2 antagonists are very potent compounds. In the early 1990s research for new drugs has moved away from potency, because profound inhibition of gastric acid secretion has been found to result in severe gastric damage, owing to the induction of elevation of gastrin levels. Since their discovery, the H_2 antagonists have quickly earned their place in the treatment of peptic ulcer disease and esophageal reflux (28, 29).

The design of H_2 antagonists has been based principally on the structure of histamine (1). Burimamide [34970-69-9], $C_9H_{16}N_4S$, the first selective H_2 receptor antagonist, was poorly absorbed after oral administration, had insufficient potency, and was rather toxic. Metiamide [34839-70-8] was more potent but caused bone marrow suppression, probably because of the presence of a thiourea group. Cimetidine (**18**), a nonthiourea congener of metiamide, was first marketed in the United Kingdom in 1976 and in the United States in 1982. Ranitidine (**20**), in which the imidazole ring of cimetidine was replaced by a dimethylaminomethylfuryl ring system, became available in 1983. Famotidine (**19**) was introduced in 1986.

For control of gastric acid secretion, the H_2 antagonists have encountered competition from the potent H^+K^+-ATPase inhibitors such as omeprazole [73590-58-6], $C_{17}H_{19}N_3O_3$ (29), which reduce acid secretion better than the H_2 antagonists.

2.3. The H_3 Receptor and Its Ligands

The first evidence for the existence of a third histamine receptor subtype was published in 1983 (7) and great advances have been made since then. The moderately active H_2 antagonist burimamide proved to be a rather potent H_3 receptor antagonist, whereas the H_2 receptor agonist impromidine (**17**) (see Table 3) is also an active H_3 antagonist (7) (Table 4). Soon after, *R*-(α)methylhistamine (**23**) and thioperamide (**27**) were described as highly potent and selective ligands for this new receptor subtype (30). These compounds are still valuable tools for receptor identification as H_3 receptor agonist and antagonist, respectively. Structural requirements for ligands of the H_3 receptor are very different from those for H_1 and H_2 receptors (8, 31).

2.3.1. H_3 Receptors

Originally described as an autoreceptor in rat brain (7), the H_3 receptor has since been reported to modulate the release of a variety of neurotransmitters and can be regarded as a general regulatory mechanism (8, 31). It is responsible for presynaptic inhibition of neurotransmitter release in CNS, and inhibition of cholinergic transmission and microvascular leakage in airways, as well as inhibition of gastric acid secretion. Moreover, the localization of this receptor subtype is not restricted to brain areas. Also, in several peripheral tissues, eg, airways, gastrointestinal (GI) tract, and heart, H_3 receptors seem to be present and exert important (patho)physiological actions (8).

2.3.2. Histamine H_3 Receptor Agonists

In contrast to the development of selective agonists for the H_1 and H_2 receptor, potent agonists for the H_3 receptor can be obtained by simple modification of the histamine molecule. Histamine itself is already a rather potent agonist of the H_3 receptor, although it is of course not very selective. Its high affinity for the H_3 receptor in comparison with its affinity for the H_1 and H_2 receptor is striking. Modification of the histamine molecule is usually not well tolerated. Substitution or replacement of the imidazole moiety is not beneficial for H_3 receptor

activity (8, 31). As for the H_2 receptor, both nitrogen atoms of the imidazole ring appear to be essential for agonistic activity (see Table 4).

Methylation of the side chain at the α-position leads to the potent and selective H_3 agonist *R*-(α)-methylhistamine (30). Yet branching the side chain at the β-position does not affect the H_3 activity, whereas α-substitution using larger substituents or two methyl groups leads to a dramatic loss of activity (8, 32). Methylation at both the α- and the β-position is also allowed and results in the potent H_3 agonist *R*-(α), *S*-(β)-methylhistamine (**24**) (8, 32). Methylation of the amine function is acceptable, although no selective agents are obtained because both N^{α},N^{α}-dimethylhistamine are also effective H_1 and H_2 agonists (8). Substitution of the amine function using larger substituents is not acceptable for potent H_3 receptor agonism.

The amine function of histamine can be replaced by other basic groups. Whereas replacement with a guanidino group results in a partial agonist, an isothioureum group appears to be suitable for agonism. The isothioureum analogue of histamine, imetit (**21**), is one of the most potent H_3 receptor agonists known (8). Moreover, it is highly selective for the H_3 receptor and is active both *in vitro* and *in vivo*. Incorporating the amine function of histamine in a piperidine ring results in immepip (**22**), another potent and selective H_3 receptor agonist. Also, this compound is highly selective for the H_3 receptor (33).

2.3.3. H_3 Receptor Antagonists

Already in 1983 it was noticed that several H_2 receptor ligands, both agonists, eg, impromidine (**17**) and dimaprit (**16**), and antagonists, eg, burimamide, were relatively potent H_3 antagonists. The H_3 antagonistic properties are, however, unrelated to the effects at the H_2 receptor. Burimamide is approximately 100-fold more active than tiotidine [69014-14-8] (base) at the H_3 receptor, whereas the reverse is observed for the H_2 receptor. H_1 antagonists do not show any appreciable effect at the H_3 receptor. In 1987 thioperamide (**27**) was introduced as the first selective and potent H_3 antagonist (30). Moreover, also for the therapeutically used betahistine (**25**), a moderate H_3 antagonism was reported. As of this writing, there are no clear ideas about the mechanism of action of betahistine, but these observations have led to the suggestion that perhaps the H_3 antagonistic effects could be involved (34). Within a series of imetit derivatives it was observed that methylation of the isothioureum moiety resulted in antagonistic properties. *N*-Substitution of the isothioureum group with aromatic groups further increased the antagonistic activity. Finally, lengthening of the side chain resulted in very potent H_3 receptor antagonists (8). Clobenpropit (**26**), which has a chlorobenzyl substituent at the isothioureum group, is approximately 10-fold more potent than thioperamide and as of this writing is the most potent H_3 antagonist known.

3. Uses of Histamine Receptor Ligands

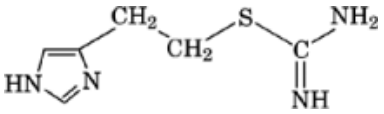
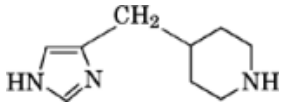
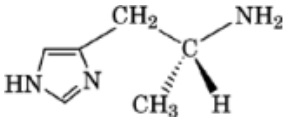
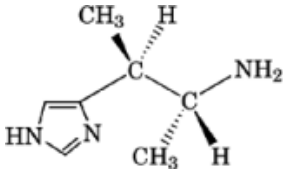
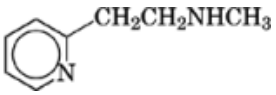
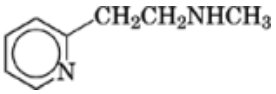
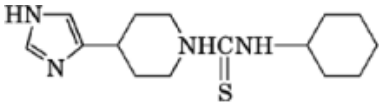
3.1. H_1 Antihistamine Treatment in Allergic Diseases

H_1-receptor antagonists are used for the symptomatic treatment of several allergic diseases where histamine release from mast cells is induced via immunological or nonimmunological mechanisms (9–11) (see also Immunotherapeutic agents).

3.1.1. Allergic Seasonal or Perennial Rhinoconjunctivitis

Histamine can cause all pathologic features of allergic rhinitis (35–37), with the exception of late-phase inflammatory reactions. Pruritus is caused by stimulation of H_1 receptors on sensory nerve endings; prostaglandins (qv) may also contribute. Sneezing, like pruritus, is an H_1-mediated neural reflex and can also be mediated by eicosanoids. Mucosal edema, which manifests as nasal obstruction, can be caused by H_1 stimulation as well as by eicosanoids and kinins. Increased vascular permeability is H_1 mediated. Nasal mucus secretion can be mediated by histamine both directly and indirectly through muscarinic discharge and by eicosanoids.

Table 4. H_3 Agonists and Antagonists

Compound	CAS Registry Number	Molecular formula	Structure	Structure number
			H_3agonists	
imetit	[102203-18-9]	$C_6H_1N_4S$		(**21**)
immepip	[151070-83-6]	$C_9H_{15}N_3$		(**22**)
R-(α)-methylhistamine	[6986-90-9]	$C_6H_1N_3$		(**23**)
R-(α), *S*-(β)-methyl-histamine	[127607-86-7]	$C_7H_{13}N_{13}$		(**24**)
			H_3 antagonists	
betahistine	[5638-76-6]	$C_8H_{12}N_2$		(**25**)
clobenpropit	[145231-45-4]	$C_{14}H_{17}N_4SCl$		(**26**)
thioperamide	[106243-16-7]	$C_{15}H_{24}N_4S$		(**27**)

Late-phase reactions, which manifest as nasal congestion and hyperirritability, are not mediated by histamine, but rather by inflammatory and chemotactic factors such as eicosanoids. In view of the excellent response to H_1 antagonists experienced by most patients with allergic rhinitis, histamine is a likely primary mediator of this disease. In numerous studies in this indication, H_1-receptor antagonists have proven to be extremely useful in ameliorating sneezing, nasal discharge, itchy nose and eyes, tearing, and eye redness. However, they are rather ineffective in relieving nasal congestion. Hence, decongestants such as pseudoephedrine or phenylpropanolamine have been added to H_1 antihistamines in order to provide relief of congestion.

3.1.2. Urticaria

The action of histamine on the skin is manifested by the classical Lewis triple response: edema (wheal), erythema (owing to direct vasodilation, redness) which spreads because of axon reflex (flare), and pruritus or pain (38, 39). Histamine, acting through its H_1 receptor, can mediate all three pathologic components of urticaria. The mechanism by which H_1 receptors mediate pruritus is indirect and involves stimulation of sensory nerve endings. Histamine-induced cutaneous vasodilation and flushing are probably partially mediated by neurohormones; other vasoactive mediators, eg, bradykinin and prostaglandins, can contribute. The partial failure of H_1 antihistamines in the treatment of urticaria may result from the involvement of other mediators or from the presence of H_2 as well as H_1 receptors in the skin. Direct vasodilation seems to involve H_2 receptors. H_3 receptors have not yet been found in human skin. Nevertheless, H_1 antihistamines remain the primary therapy for urticaria; these reduce pruritus and the number, size, and duration of urticarial lesions.

3.1.3. Asthma

In asthma, bronchospasm and mucosal edema can be caused by H_1 receptor stimulation. H_2 and possibly H_1 activation may be minor causes of mucus secretion. However, other mediators, such as leukotrienes, prostaglandins, bradykinin, and PAF, may be more important in asthma than histamine. Airway inflammation is not stimulated by histamine but can be caused by inflammatory factors, such as chemotactic factors. Mucus glycoprotein secretion can be induced by H_2 receptor activation, whereas increased movement of interstitial fluid into the airway lumen can be mediated by H_1 receptors. Clinical trials using classical H_1 antagonists for the treatment of asthma have yielded disappointing results. The drug concentrations achieved in the lungs with the available H_1 antagonists may not be high enough for an effective H_1 receptor blockade. H_1 antihistamines provide some relief from seasonal or chronic asthma when taken over weeks or months by patients with mild asthma, but these certainly are not drugs of first choice (40, 41). High dose nonsedating H_1 antagonists, however, deserve further study as potential agents in the treatment of asthma.

3.1.4. Anaphylaxis

All the symptoms of anaphylaxis can be reproduced by histamine. Vascular permeability manifests as angioedema, and laryngeal and intestinal edema; vasodilation leads to flushing and headache; smooth muscle contraction results in wheezing, abdominal cramping, and diarrhea. Tachycardia, often in the form of palpitations, can be caused by decreased atrioventricular node conduction time and indirectly by histamine-induced vasodilation and resultant catecholamine secretion. Reduced peripheral vascular resistance is responsible for syncope. Mucus secretion manifests as rhinorrhea and bronchorrhea. In acute anaphylaxis, treatment of first choice is epinephrine; H_1 receptor antagonists are a useful adjunctive treatment for control of pruritus, rhinorrhea, and some other symptoms (21).

3.1.5. Atopic Dermatitis

The mechanism of itching associated with atopic dermatitis remains unknown, but histamine is almost certainly involved to some extent as histamine concentrations are increased in the skin and in the plasma of patients with this disorder (39, 42). Second-generation H_1 receptor antagonists, unlike first-generation H_1

receptor antagonists, have not been uniformly found to be effective in relieving itching in atopic dermatitis, which may be related to the absence of a sedative effect (43).

3.2. Clinically Efficacy and Side-Effects of H_1 Antihistamines

3.2.1. Clinically Efficacy

It is evident from the mechanism of action of antihistamines and the etiology of allergic diseases that antihistamines in no sense achieve a cure of the patient's allergy. After the administration of a therapeutic dose, a temporal blockade of the effects of histamine is obtained. Whereas classical antihistamines needed at least twice daily administration, for most of the more recently introduced agents administration once daily is sufficient.

Nevertheless, although the nonsedating H_1 antihistamines have substantially improved the acceptability and clinical efficacy of this class of compounds, these do not provide complete relief; eye disease responds less well than nasal disease, of the rhinitis symptoms nasal congestion responds poorly, breakthrough symptoms occur at high pollen counts, and only some 70% of patients report excellent to good treatment responses. Considerable research therefore still continues in the H_1 antihistamine field. New antihistamines are continually being introduced.

3.2.2. Side Effects

The classical H_1 antihistamines are not very specific, and several compounds have some degree of anticholinergic activity, eg, diphenhydramine; serotonin antagonism, eg, cyproheptadine; or adreno-receptor blocking activity, eg, promethazine. Anticholinergic effects can present side effects such as dry mouth, blurred vision, and urine retention, whereas the anticholinergic action of some antihistamines is probably the reason for effectiveness in motion sickness (19). Interactions in the brain with noradrenergic, serotonergic, and dopaminergic uptake systems may play a role in behavioral effects of H_1 antihistamines.

At therapeutic doses, the classical H_1-receptor antagonists generally produce sedation. This usually unwanted effect is probably caused by the H_1-receptor blockade in the CNS. Among the conventional antihistamines, the aminoalkylethers, eg, diphenhydramine, and phenothiazines, eg, promethazine, have the most prominent sedative effects (promethazine is widely used as a hypnotic agent), whereas the alkylamines seem to cause less CNS depression. Sedation is often transient, owing to the development of tolerance, but may be sufficient to persuade the patient to discontinue treatment. Patients vary considerably in susceptibility to the sedating effects of antihistamines, but on average sedation using classical H_1 antagonists has been reported in some 20% of users.

The second-generation H_1 antihistamines, such as terfenadine (**9**), astemizole (**10**), cetirizine (**4**), and loratadine (**7**), generally present few side effects and, in particular, are considered not to cause sedation, mainly because of reduced ability to penetrate the CNS. However, terfenadine (**9**) and astemizole (**10**), the two most widely used nonsedating antihistamines available in the United States, have been associated with prolongation of the QT-interval in the electrocardiogram (ECG) and ventricular arrhythmias. The pharmacodynamic mechanism is unclear, but may be related to inhibition of the delayed potassium rectifier current (44). The QT prolongation generally occurs at higher than therapeutic plasma levels. This can be the case with overdoses or in combination with drugs that impair hepatic metabolism, eg, azole antimycotics (see Antiparasitic agents, antimycotics) and macrolide antibiotics (qv). It remains to be seen whether this side effect is particular to terfenadine and astemizole or whether it may be a class effect of antihistamines which may also become apparent with the more recently introduced antihistamines after more widespread exposure.

3.2.3. Topical Application

Azelastine (**11**) and levocabastine (**13**) have been developed for topical application (45). The topical antihistamines address the preference of some patients for a local treatment and allow administration of drug directly

to the site required. The advantage of this therapeutic approach is likely to be in the speed of onset of symptom relief. In contrast to earlier reports of sensitization with older antihistamines locally applied to the skin (46), sensitization has not been reported with local application to the nose or eyes.

3.3. Selective H_3 Agonists and Antagonists

No clear therapeutic indications have been reported for H_3 receptor ligands. Yet, with the development of highly potent and selective agonists and antagonists, insights in the role of histamine H_3 receptors in various (patho)physiological processes have been obtained. An interesting option for therapeutic application of H_3 agonists would be in asthmatic diseases (8). H_3 receptors are known to be present in guinea pig and human airways, where they can inhibit nonadrenergic/noncholinergic (NANC) and cholinergic neurotransmission (8). Moreover, H_3 agonists can inhibit *in vivo* the microvascular leakage often associated with neurogenic airway inflammation. Using sensitized guinea pigs (47), thioperamide (**27**) was shown to enhance the allergen-induced bronchoconstriction in ovalbumine-sensitized animals. This bronchoconstriction resulted from H_1 receptor stimulation after histamine release from mast cells. These data indicate that H_3 receptors might be present on mast cells and could regulate the release of histamine. Previously, the H_3 receptor was indeed suggested to be involved in the regulation of histamine synthesis in lung tissue (30). Therapeutic application of H_3 receptor agonists could also be envisaged for gastrointestinal disorders. H_3 receptors are present throughout the GI tract and inhibit again the NANC and cholinergic neurotransmission (8). These properties could become useful for the treatment of diarrhea. Moreover, H_3 receptors also control gastric acid release, although some marked species dependence is noticed (8). However, application of H_3 agonists in this area does not seem to be probable; the H_2 antagonists and the proton pump inhibitors serve quite well.

Because histamine in the CNS is important for the regulation of sleep/wakefulness, applications in this area could be found. In cats, the H_3 receptor has been shown to affect the sleep pattern, and it has also been implicated in this respect in rats and mice (8).

4. Economic Aspects

The sales of antagonists of H_1 receptors, eg, diphenhydramine, terfenadine, and astemizole, used in the treatment of allergic diseases, represent 1% of the overall pharmaceutical market, ie, $1.7 billion (U.S.). H_2 antagonists, eg, cimetidine and ranitidine, are effective in peptic ulcer disease and esophageal reflux. Sales represent 3.5% of the world market, ie, $6 billion (U.S.). H_3 agonists or antagonists have not yet found a clear indication.

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