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International Union of Pharmacology. XIII. Classification of Histamine Receptors

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I. Introduction and Historical Perspective

The classification of histamine receptors has to date been based on rigorous classical pharmacological analysis, and as yet, the classification of the three histamine receptors that have been defined by this process, (i.e., the H_1-, H_2-, and H_3-receptors) have not been added to because of more recent molecular biological approaches (Schwartz et al., 1991, 1995; Hill, 1990; Leurs et al., 1995b). The scant number of known histamine receptors, compared with the plethora of receptors for some other endogenous substances, probably reflects the relative neglect of histamine rather than a paucity of its receptors. There is some preliminary evidence of heterogeneity of the known histamine receptors (which will be reviewed later in this article), but the acceptance of additional subtypes still awaits the identification of "sequence differences" within a single species and the development of selective agonists and antagonists providing the structural, recognition, and transductional information necessary for reliable classification.

The first histamine receptor antagonists (popularly referred to as the classical antihistamines but now called H_1-receptor antagonists) were synthesized (Bovet and Staub, 1936; Bovet, 1950) over 20 years after the discovery (Barger and Dale, 1910) and descriptions of some of the physiological effects (Dale and Laidlaw, 1910) of histamine. These accomplishments had been preceded, as for some other endogenous biogenic amines, by its synthesis as a chemical curiosity (Windaus and Vogt, 1907). Early studies of the antihistamines were qualitative, for example, the demonstration of their ef-

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fectiveness in protecting against bronchospasm produced in guinea pigs by anaphylaxis or administration of histamine (Bovet and Staub, 1936). Though qualitative, these studies yielded compounds, e.g., mepyramine (pyrilamine), that remain major ligands to define histamine receptors.

These antagonists were shown to reduce the effects of histamine on many tissues, notably vascular and extravascular smooth muscle (e.g., guinea pig ileum), but it became apparent that some of the effects of histamine were refractory to these classical antihistamines (Loew, 1947). For example, histamine-stimulated gastric secretion was shown to be unresponsive to three different antihistamines (Ashford et al., 1949). The vasodilator response to histamine in the cat was shown to be only partly sensitive to an antihistamine, leading to the suggestion that histamine causes vasodilatation by combining with more than one receptor (Folkow et al., 1948). The application of the method of Schild (Arunlakshana and Schild, 1959) to the classification of receptors revealed that the pA_2 ($-\log K_B$) value of mepyramine for antagonism of the positive chronotropic effect of histamine on the right atrium of the guinea pig differed from mepyramine's pA_2 value for antagonism of the contractile response to histamine in guinea pig ileum, implying that the receptors involved were distinct (Arunlakshana and Schild, 1959; Trendelenburg, 1960). The histamine receptor in guinea pig ileum and in other tissues that showed the same or similar pA_2 value for these early antihistamines was then named the H_1-receptor (Ash and Schild, 1966). As the relative potencies of these histamine antagonists and histamine agonists on gastric acid secretion, relaxation of rat uterus, and chronotropy of the guinea pig right atrium differed from those on the H_1-receptor, it was concluded that a separate histamine receptor was involved in these responses.

The development of specific antagonists (H_2-antagonists) for this novel receptor represents a classic example of rational drug design (Black et al., 1972; Black, 1989) and showed the "practical value" (Green and Maayani, 1987; Jenkinson, 1987) of a quantitative approach to the analysis of receptor antagonism (Arunlakshana and Schild, 1959). Burimamide was the first compound to be described (Black et al., 1972) that had a higher pA_2 for antagonism of the histamine-mediated responses on guinea pig atrium and rat uterus than the pA_2 determined for antagonism of the contractile response to histamine in guinea pig ileum. Burimamide was also able to reduce gastric acid secretion in dogs and humans and to reduce the blood pressure response of the cat to histamine (Black et al., 1972). A large number of more potent and selective H_2-receptor antagonists have since been developed (Cooper et al., 1990), although further quantitative investigations of the antagonist potency of burimamide on other histamine-mediated responses contributed to the definition and classification of the histamine H_3-receptor (Arrang et al., 1983).

The third histamine receptor was also defined by a functional assay. Histamine was found to inhibit its own synthesis and release in rat cerebral cortical slices, and the effects of H_1- and H_2- receptor agonists and antagonists indicated a distinct receptor (Arrang et al., 1983, 1987b). A highly selective agonist, R-(α)-methylhistamine, and antagonist, thioperamide, clearly defined the H_3-receptor (Arrang et al., 1987). Since that time, considerable efforts have been made to develop other H_3-receptor–selective agonists and antagonists (Garbarg et al., 1992; Jansen et al., 1992; Van der Goot et al., 1992; Vollinga et al., 1994; Ganellin et al., 1995; Ligneau et al., 1995; Stark et al., 1996b,c).

Table 1 summarizes some of the operational characteristics used to define the nature of the histamine receptor involved in different tissue responses. Histamine derivatives are numbered according to the system given in figure 1 (Black and Ganellin, 1974).

II. Histamine H_1-Receptor

A. Distribution and Function

The study of the distribution of histamine H_1-receptors in different mammalian tissues has been greatly aided by the development of selective radioligands for this particular histamine receptor subtype. [^{3}H]mepyramine was originally developed in 1977 (Hill et al., 1977) and since that time has been used successfully to detect H_1-receptors in a wide variety of tissues including: mammalian brain; smooth muscle from airways, gastrointestinal tract, genitourinary system, and the cardiovascular system; adrenal medulla; and endothelial cells and lymphocytes (Hill, 1990). In some tissues and cells, however, it is notable that [^{3}H]mepyramine additionally binds to secondary non-H_1–receptor sites (Chang et al., 1979a; Hill and Young, 1980; Hadfield et al., 1983; Mitsuhashi and Payan, 1988; Arias-Montano and Young, 1993; Dickenson and Hill, 1994; Leurs et al., 1995b). In rat liver, in which [^{3}H]mepyramine predominantly binds to a protein homologous with debrisoquine 4-hydroxylase cytochrome P450 (Fukui et al., 1990), quinine can be used to inhibit this nonspecific binding. This observation has led Liu et al. (1992) to suggest that quinine may be used to inhibit binding to other lower affinity sites. However, it is clear that not all secondary binding sites for [^{3}H]mepyramine are sensitive to inhibition by quinine (Dickenson and Hill, 1994). Thus, in DDT_1MF-2 cells, a 38 to 40 kDa protein has been isolated, which binds H_1-receptor antagonists with K_D values in the micromolar range (Mitsuhashi and Payan, 1988, Mitsuhashi et al., 1989) but which is not sensitive to inhibition by quinine (Dickenson and Hill, 1994). Nevertheless, DDT_1MF-2 cells can be shown to additionally possess [^{3}H]mepyramine binding sites that have the characteristics of H_1-receptors (i.e., K_D values in the nanomolar range) and to mediate functional responses, which are clearly produced by histamine H_1-receptor

TABLE 1
Operational characteristics of histamine receptors

Receptor	Location	Response	Agonists	Antagonists
Histamine H_1	Most smooth muscle, endothelial cells, adrenal medulla, heart, CNS	Smooth muscle contraction, stimulation of NO formation, endothelial cell contraction, increased vascular permeability, stimulation of hormone release, negative inotropism, depolarization (block of leak potassium current) and increased neuronal firing, inositol phospholipid hydrolysis and calcium mobilization, hyperpolarization by Ca^{2+}-dependent potassium current	Histamine[a] 2-[3-(Trifluoromethyl)-phenyl]histamine 2-Thiazolylethylamine 2-Pyridylethylamine 2-Methylhistamine	Mepyramine (+) and (−) Chlorpheniramine Triprolidine Temelastine Diphenhydramine Promethazine
Histamine H_2	Gastric parietal cells, vascular smooth muscle, suppressor T cells, neutrophils, CNS, heart, uterus (rat)	Stimulation of gastric acid secretion, smooth muscle relaxation, stimulation of adenylyl cyclase, positive chronotropic and inotropic effects on cardiac muscle, decreased firing rate, hyperpolarization or facilitation of signal transduction in CNS, block of Ca^{2+}-dependent potassium conductance (I AHP, accommodation of firing, after-hyperpolarization), increase of hyperpolarization-activated current, inhibition of lymphocyte function	Histamine[a] Amthamine Dimaprit Impromidine[b] Arpromidine[b]	Cimetidine Ranitidine Tiotidine Zolantidine Famotidine
Histamine H_3	CNS, peripheral nerves (heart, lung, gastrointestinal tract), endothelium, enterochromaffin cells	Inhibition of neurotransmitter release, endothelium-dependent relaxation of rabbit middle cerebral artery, inhibition of gastric acid secretion (dog), increase in smooth muscle voltage-dependent Ca^{2+} current, inhibition of firing of tuberomammilary (histaminergic) neurons	Histamine[a] R-α-methylhistamine Imetit Immepip N^{α}-methylhistamine[a]	Thioperamide Clobenpropit Iodophenpropit Iodoproxyfan

CNS, central nervous system.
[a] Nonselective.
[b] H_3-antagonist.

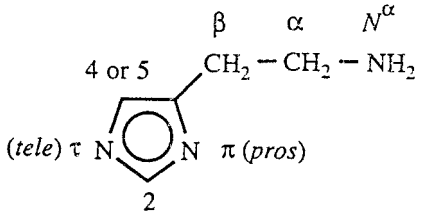


FIG. 1. Numbering for histamine derivatives.

activation (Dickenson and Hill, 1992; White et al., 1993; Dickenson and Hill, 1994).

Other radioligands that have been used to study histamine H_1-receptors are [^{3}H]mianserin (Peroutka and Snyder, 1981), [^{3}H]doxepin (Tran et al., 1981; Kamba and Richelson, 1984; Taylor and Richelson, 1982), [^{125}I]iodobolpyramine (Bouthenet et al., 1988), [^{125}I]iodoazidophenpyramine (Ruat et al., 1988), and [^{3}H](+)-N-methyl-4-methyldiphenhydramine (Treherne and Young, 1988b). [^{125}I]Iodobolpyramine has been used for autoradiographic localization of H_1-receptors in guinea pig brain, although less success has been achieved in rat brain (Körner et al., 1986; Bouthenet et al., 1988). The very slow dissociation of [^{3}H]mepyramine from H_1-receptors at low temperatures (e.g., 4°C) does, however, mean that this ligand can also be used for autoradiography (Palacios et al., 1981a,b; Rotter and Frostholm, 1986). [^{125}I]Iodoazidophenpyramine is a very potent H_1-receptor antagonist that can bind irreversibly to H_1-receptors following irradiation with ultraviolet light (Ruat et al., 1988). [^{11}C]Mepyramine and [^{11}C]doxepin have also proved useful for imaging histamine H_1-receptors in the living human brain (Villemagne et al., 1991; Yanai et al., 1992, 1995).

H_1-receptors have been extensively studied in blood vessels (Barger and Dale, 1910; Dale and Laidlaw, 1910; Folkow et al., 1948; Black et al., 1972) and other smooth muscle preparations (Ash and Schild, 1966; Black et al., 1972; Marshall, 1955; Hill, 1990). In smooth muscles, such as the guinea pig ileum, which freely generate muscle action potentials, modulation of action-potential discharge by low concentrations of histamine is an important mechanism by which tension is increased (Bolton, 1979; Bolton et al., 1981; Bülbring and Burnstock, 1960). In guinea pig ileum, there is also evidence

that a component of the contractile response to histamine is mediated by inositol 1,4,5-trisphosphate–induced mobilization of intracellular calcium (Morel et al., 1987; Bolton and Lim, 1989; Donaldson and Hill, 1986b). In nonexcitable smooth muscles, such as airway and vascular smooth muscle, contractile responses to H_1-receptor stimulation primarily involve mobilization of calcium from intracellular stores as a consequence of inositol phospholipid hydrolysis (Matsumoto et al., 1986; Kotlikoff et al., 1987; Takuwa et al., 1987; Hall and Hill, 1988; Paniettieri et al., 1989; Van Amsterdam et al., 1989).

In vascular endothelial cells, H_1-receptor stimulation leads to several cellular responses including: (*a*) changes in vascular permeability (particularly in postcapillary venules) as a result of endothelial cell contraction (Majno and Palade, 1961; Majno et al., 1968; Meyrick and Brigham, 1983; Grega, 1986; Killackey et al., 1986; Svensjo and Grega, 1986); (*b*) prostacyclin synthesis (McIntyre et al., 1985; Brotherton, 1986; Carter et al., 1988; Resink et al., 1987); (*c*) synthesis of platelet-activating factor (McIntyre et al., 1985); (*d*) release of Von Willebrand factor (Hamilton and Sims, 1987); and (*e*) release of nitric oxide (Van De Voorde and Leusen, 1993; Toda, 1984). The H_1-receptor has also been characterized on human T lymphocytes using [^{125}I]iodobolpyramine (Villemain et al., 1990) and shown to increase $[Ca^{2+}]_i$ (Kitamura et al., 1996).

Histamine H_1-receptors have long been established to be present in the adrenal medulla and to elicit the release of catecholamines (Emmelin and Muren, 1949; Staszewska-Barczak and Vane, 1965; Robinson, 1982; Livett and Marley, 1986; Noble et al., 1988). Thus, histamine can induce the release of both adrenaline and noradrenaline from cultured bovine adrenal chromaffin cells (Livett and Marley, 1986). In these cells, histamine can also stimulate phosphorylation of the catecholamine biosynthesis enzyme tyrosine hydroxylase via a mechanism that involves release of intracellular calcium (Bunn et al., 1995). In addition to its effects on catecholamine synthesis and release from adrenal chromaffin cells, histamine can also elicit the release of leucine- and methionine-enkephalin (Bommer et al., 1987). Furthermore, after prolonged exposure to histamine, there is a marked increase in messenger ribonucleic acid-encoding proenkephalin A (Bommer et al., 1987; Kley, 1988; Wan et al., 1989).

In human atrial myocardium and guinea pig ventricle, histamine produces negative inotropic effects (Guo et al., 1984; Genovese et al., 1988; Zavecz and Levi, 1978). In human myocardium, this response is associated with inhibitory effects on heart rate and can be unmasked when the positive effects of histamine on the rate and force of contraction (mediated via H_2-receptors) are attenuated by conjoint administration of adenosine or adenosine A_1-receptor agonists (Genovese et al., 1988). However, in guinea pig left atria (Reinhardt et al., 1974, 1977; Steinberg and Holland, 1975; Hattori et al., 1983, 1988a) and rabbit papillary muscle (Hattori et al., 1988b), histamine produces a positive inotropic response via a mechanism that is not associated with a rise in adenosine 3c,5c-cyclic monophosphate (cAMP[b]) levels (see Hill, 1990).

Histamine H_1-receptors are widely distributed in mammalian brain (Hill, 1990; Schwartz et al., 1991). In human brain, higher densities of H_1-receptors are found in neocortex, hippocampus, nucleus accumbens, thalamus, and posterior hypothalamus, whereas cerebellum and basal ganglia show lower densities (Chang et al., 1979b; Kamba and Richelson, 1984; Martinez-Mir et al., 1990; Villemagne et al., 1991; Yanai et al., 1992). The distributions in rat (Palacios et al., 1981a) and guinea pig (Palacios et al., 1981b; Bouthenet et al., 1988) are similar to each other and to humans with the exception that the guinea pig cerebellum shows high density (Ruat and Schwartz, 1989; Chang et al., 1979b; Hill and Young, 1980; Palacios et al., 1981b; Bouthenet et al., 1988). In most brain areas, there was overlap of H_1-receptor binding sites and messenger ribonucleic acid levels except in hippocampus and cerebellum in which the discrepancy is likely to reflect the presence of abundant H_1-receptors in dendrites of pyramidal and Purkinje cells, respectively (Traiffort et al., 1994). Histamine H_1-receptor activation causes inhibition of firing and hyperpolarization in hippocampal neurons (Haas, 1981) and an apamine-sensitive outward current in olfactory bulb interneurons (Jahn et al., 1995), effects most likely produced by intracellular Ca^{2+} release. However, many other notably vegetative ganglia (Christian et al., 1989), hypothalamic supraoptic (Haas et al., 1975), brainstem (Gerber et al., 1990; Khateb et al., 1990), thalamic (McCormick and Williamson, 1991), and human cortical neurons (Reiner and Kamondi, 1994) are excited by histamine H_1-receptor activation through a block of a potassium conductance.

B. H_1-Selective Ligands

Although a large number of compounds have been synthesized as selective and competitive antagonists of the histamine H_1-receptor (see for example Casy, 1977; Ganellin, 1982), chemical effort directed at the generation of highly potent and selective H_1-receptor agonists has not achieved the same success. Modification of the ethylamine side chain of histamine is not favorable for H_1-receptor agonism (Leurs et al., 1995b). Furthermore, resolution of the enantiomers of the chiral compounds generated by methylation of the α- or β-positions did not reveal any stereoselectivity of the side chain for the H_1-receptor (Arrang et al., 1987; Leurs et al., 1995). Alkylation of the side chain amine group does not dras-

[b] Abbreviations: cAMP, cyclic adenosine 3c,5c-cyclic monophosphate; cNDA, complementary deoxyribonucleic acid; CNS, central nervous system; DPPE, N-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine; GTPγS, guanosine 5′*O*-(3-thiotriphosphate); NMDA, N-methyl-D-aspartate; TM, transmembrane.

tically reduce H_1-receptor activity, but N^{α}- and N^{α},N^{α}-dimethylhistamine are also potent agonists for the H_3-receptor (table 2; fig. 2; Arrang et al., 1983). Modification of the imidazole moiety of histamine has been the most successful approach for obtaining agonists with selectivity for the H_1-receptor. Replacement of the imidazole moiety of histamine by other aromatic heterocyclic ring structures in 2-pyridylethylamine and 2-thiazolylethylamine yields two compounds with selectivity for the H_1-receptor (table 2; fig. 2). Both compounds act as full agonists in producing contraction of guinea pig ileum (Donaldson and Hill, 1986c), but in other tissues (e.g., guinea pig cerebral cortical slices or DDT_1MF-2 cells), 2-pyridylethylamine behaves as a low-efficacy agonist (Donaldson and Hill, 1986a; White et al., 1993). Substitutions in the 2-position of the imidazole ring of histamine have produced compounds that are the most selective H_1-agonists available (Zingel et al., 1995). Thus, 2(3-bromophenyl)histamine and 2[3-(trifluoromethyl)-phenyl]histamine are both relatively potent and highly selective H_1-agonists (table 2; fig. 2; Leschke et al., 1995). Both compounds appear to be potent H_1-agonists in guinea pig ileum (Leschke et al., 1995), although some of the halogenated 2-phenylhistamines are low-efficacy agonists in DDT_1MF-2 cells (Zingel et al., 1990; White et al., 1993) and in guinea pig aorta (Leschke et al., 1995) and can exhibit partial agonist properties.

TABLE 2
Agonist potency ratios of histamine receptors

Histamine	H_1 100	H_2 100	H_3 100
2-(3-(Trifluoromethyl)phenyl)-histamine	128[a]	<0.1[a]	n.d.
2-(3-Bromophenyl)histamine	112[a]	<0.1[a]	n.d.
N^{α}-methylhistamine	72[b]	74[c]	270[d]
2-(2-Thiazolyl)ethylamine	26[b]	2.2[b]	<0.008[d]
2-Methylhistamine	17[c]	4[c]	<0.08[d]
2-(2-Pyridyl)ethylamine	5.6[b]	2.5[b]	n.d.
Arpromidine	Antagonist[e]	10,230[e]	
Impromidine	Antagonist[f]	4,810[f]	Antagonist[d,o]
Sopromidine	2[g]	740[g]	Antagonist[h,p]
Amthamine	1[i]	150[i]	0.002[i]
Dimaprit	<0.0001[j]	71[j]	Antagonist[d,q]
4-Methylhistamine	0.2[c]	43[c]	<0.008[d]
Imetit	<0.1[k]	0.6[k]	6200[k]
Immepip	n.d.	n.d.	2457[l]
R-α-methylhistamine	0.5[m]	1[m]	1550[m]
S-α-methylhistamine	0.5[b]	1.7[b]	13[m]
R-α,S-β-dimethylhistamine	0.07[n]	0.1[n]	1800[n]

Values determined from guinea pig ileum contraction (H_1), guinea pig atrium (chronotropic stimulation, H_2), and inhibition of K^+-stimulated histamine release from rat cerebral cortical slices (H_3), or inhibition of electrically stimulated contraction of guinea pig ileum (H_3). n.d., not determined.

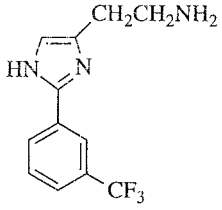
[a] Leschke et al. (1995) [g] Elz et al. (1989) [m] Arrang et al. (1987)
[b] Ganelin (1982) [h] Arrang et al. (1985c) [n] Lipp et al. (1992)
[c] Black et al. (1972) [i] Eriks et al. (1992) [o] See table 4.
[d] Arang et al. (1983) [j] Durant et al. (1977) [p] K_B = 56 nM.
[e] Sellier et al. (1992) [k] Garbarg et al. (1992) [q] K_B = 3 μM.
[f] Durant et al. (1978) [l] Vollinga et al. (1994)

Mepyramine (also known as pyrilamine) is the reference selective and high-affinity H_1-receptor antagonist (table 3; Hill, 1990). Other classical H_1-antagonists that have been used for characterization purposes include chlorpheniramine, tripelennamine, promethazine, and diphenhydramine (fig. 3). Some of these, however, possess marked muscarinic receptor antagonist properties (Hill, 1990, 1987), and consequently the selectivity of these compounds between the three different histamine receptors (table 3) does not guarantee an unambiguous characterization. This can only be achieved by appropriate quantitative assessment of receptor antagonism, preferably with a range of compounds of very different chemical structure. The stereoisomers of chlorpheniramine are particularly useful in this regard (table 3). The enantiomers of 4-methyl-diphenhydramine and brompheniramine also differ by two orders of magnitude in their affinity for the H_1-receptor (Chang et al., 1979b; Treherne and Young, 1988b). The geometric isomer trans-triprolidine is three orders of magnitude more potent than its cis counterpart and is one of the most potent H_1-antagonists available for the guinea pig H_1-receptor (tables 3 and 4; Ison et al., 1973). The tricyclic antidepressants amitriptyline and doxepin are also very potent H_1-receptor antagonists (K_D 0.6 and 0.1 nM respectively; Figge et al., 1979; Aceves et al., 1985).

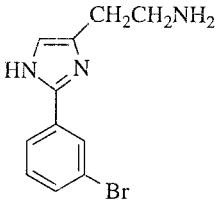
At therapeutic dosages, many of the classical H_1-antihistamines give rise to sedative side effects that have been attributed to occupancy of H_1-receptors in the central nervous system (CNS) (Schwartz et al., 1981; Nicholson et al., 1991; Leurs et al., 1995b). Most of the classical H_1-antihistamines, including promethazine and (+)-chlorpheniramine, readily cross the blood-brain barrier. However, several compounds that penetrate poorly into the CNS and appear to be devoid of central depressant effects are now available (fig. 4). These include terfenadine (Rose et al., 1982; Wiech and Martin, 1982), astemizole (Laduron et al., 1982; Niemegeers et al., 1982), mequitazine (Uzan and Le Fer, 1979), loratadine (Ahn and Barnett, 1986), acrivastine (Leighton et al., 1983; Cohen et al., 1985), cetirizine (Timmerman, 1992b), and temelastine (Brown et al., 1986; Calcutt et al., 1987). The pK_i values for these agents are given in table 5 (Ter Laak et al., 1994).

C. Receptor Structure

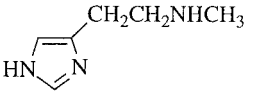
Photoaffinity binding studies using [^{125}I]iodoazidophenpyramine and subsequent sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis have indicated that the H_1-receptor protein has a molecular weight of 56 kDa under reducing conditions in rat, guinea pig, and mouse brain (Ruat et al., 1988, 1990b; Ruat and Schwartz, 1989). Similarly, studies in bovine adrenal medullar membranes with another photoaffinity ligand [^{3}H]azidobenzamide (Yamashita et al., 1991b)



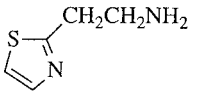
2-(3-Trifluoromethyl phenyl)histamine



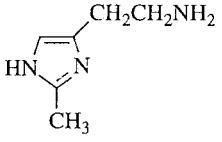
2-(3-Bromophenyl)-histamine



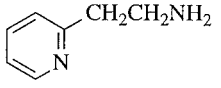
Nα-Methylhistamine



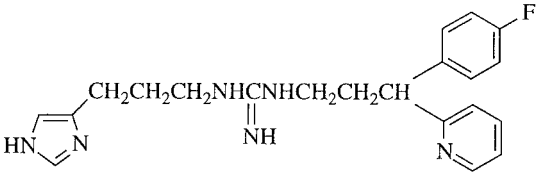
2-(2-Thiazolylethyl)amine



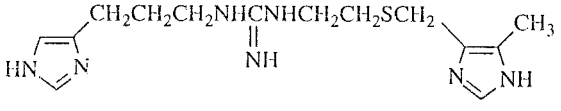
2-Methylhistamine



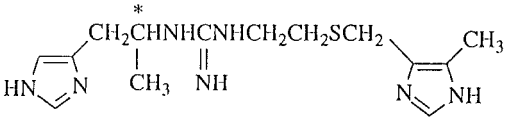
2-(2-Pyridylethyl)amine



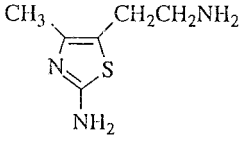
Arpromidine



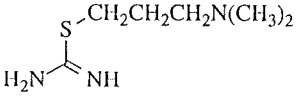
Impromidine



Sopromidine (* :R chirality)



Amthamine



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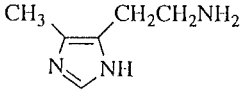
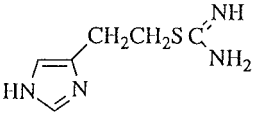


4-Methylhistamine



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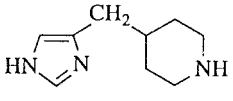

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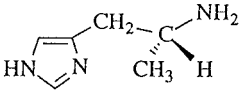
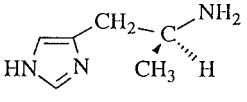
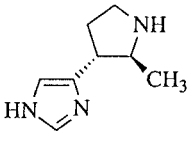


(R)-α-Methylhistamine



(S)-α-Methylhistamine



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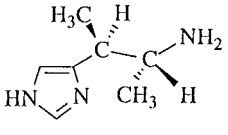

(Rα, Sβ)-α,β-Dimethylhistamine

FIG. 2. Histamine receptor agonists (H_1, H_2, and H_3).

found labeled peptides in the size range 53 to 58 kDa. Interestingly, the specifically labeled H_1-receptor (with [^{125}I]iodoazidophenpyramine) in guinea pig heart was found to have a substantially higher molecular weight, although there is no obvious difference in the pharmacological characteristics of the H_1-receptor in this tissue (Ruat et al., 1990a).

The bovine adrenal medulla H_1-receptor was cloned in 1991 by expression cloning in the *Xenopus* oocyte system (Yamashita et al., 1991a). The deduced amino acid se-

TABLE 3
Antagonist dissociation constants at histamine receptors

	K_B values		
	H_1	H_3	H_2
Doxepin	0.06 nM[a]	n.d.	n.d.
Triprolidine (trans)	0.1 nM[b]	n.d.	n.d.
Temelastine	0.3 nM[c]	>10 μM[c]	n.d.
Mepyramine (pyrilamine)	0.4 nM[d]	5.2 μM[e]	>1 μM[f]
(+)-Chlorpheniramine	0.4 nM[g]	1.2 μM[h]	>58 nM[i]
(−)-Chlorpheniramine	204 nM[g]	1.2 μM[h]	>58 nM[i]
Diphenhydramine	1.0 nM[j]	n.d.	n.d.
Promethazine	1.2 nM[k]	3.0 μM[l]	n.d.
Chlorpromazine	1.2 nM[k]	5.9 μM[l]	n.d.
Tripelenamine	3.2 nM[d]	n.d.	n.d.
Arpromidine	20 nM[m]	agonist[ah]	
Cimetidine	450 μM[n]	800 nM[n]	33 μM[i]
Metiamide	n.d.	920 nM[o]	2.5 μM[j]
Ranitidine	>100 μM[p]	200 nM[p]	>1.2 μM[i]
Famotidine	n.d.	17 nM[q]	n.d.
Zolantidine	6.2 μM[r]	25 nM[r]	>10 μM[s]
Mifentidine	>24 μM[t]	24 nM[t]	100 nM[s]
Tiotidine	>30 μM[u]	15 nM[v]	>12 μM[i]
Iodoaminopotentidine	1.1 μM[w]	2.5 nM[w]	n.d.
Impromidine	3.4 μM[x]	agonist[x]	65 nM[i]
Burimamide	320 μM[y]	7.8 μM[z]	70 nM[i]
Thioperamide	>100 μM[aa]	>10 μM[aa]	4 nM[aa]
Iodophenpropit	n.d.	n.d.	0.25 nM[ab]
Clobenpropit	>10 μM[ac]	>10 μM[ac]	0.13 nM[ac]
Iodoproxyfan	1.4 μM[ad]	5.3 μM[ad]	5 nM[ad, ag]
Impentamine	126 μM[ae]	250 μM[ae]	4 nM[ae]
GR174737	>10 μM[af]	>10 μM[af]	8 nM[af]

Values determined in functional assays from guinea pig ileum contraction (H_1), biochemical determinations in guinea pig cerebral cortical slices (H_1), chronotropic responses in guinea pig atria (H_2), cyclic AMP accumulation in guinea pig hippocampal slices (H_2), inhibition of histamine release in rat cerebral cortical slices (H_3), and inhibition of transmurally stimulated guinea pig ileum (H_3). n.d., not determined.

[a] Figge et al. (1979)
[b] Ison et al. (1973)
[c] Brown et al. (1986)
[d] Marshall (1955)
[e] Trendelenburg (1960)
[f] Hew et al. (1990)
[g] Hill et al. (1981)
[h] Hill (1990)
[i] Arrang et al. (1983)
[j] Ganellin (1982)
[k] Hill and Young (1981)
[l] Tuong et al. (1980)
[m] Sellier et al. (1992)
[n] Brimblecombe et al. (1975)
[o] Black et al. (1974)
[p] Cavanagh et al. (1983)
[q] Takeda et al. (1982)
[r] Calcutt et al. (1988)
[s] Schwartz et al. (1990)
[t] Donetti et al. (1984)
[u] Donaldson et al. (1988)
[v] Yellin et al. (1979)
[w] Hirschfeld et al. (1992)
[x] Durant et al. (1978)
[y] Buschauer et al. (1992)
[z] Black et al. (1972)
[aa] Arrang et al. (1987)
[ab] Jansen et al. (1992)
[ac] Van der Goot et al. (1992)
[ad] Ligneau et al. (1994)
[ae] Vollinga et al. (1995)
[af] Clitherow et al. (1996)
[ag] Stark et al. (1996a)
[ah] Buschauer (1989)

quence represents a 491 amino acid protein with a calculated molecular weight of 56 kDa (table 6). The protein has the seven putative transmembrane (TM) domains expected of a G-protein–coupled receptor and possesses N-terminal glycosylation sites. A striking feature of the proposed structure is the very large third intracellular loop (212 amino acids) and relatively short (17 amino acids) intracellular C terminal tail. The availability of the bovine sequence and lack of introns has enabled the H_1-receptor to be cloned from several species (table 6) including rat (Fujimoto et al., 1993), guinea pig (Horio et al., 1993; Traiffort et al., 1994), mouse (Inove et al., 1996), and human (De Backer et al., 1993; Fukui et al., 1994; Moguilevsky et al., 1994; Smit et al., 1996c). The human histamine H_1-receptor gene has now been localized to chromosome 3 bands 3p14-p21 (Le Coniat et al., 1994).

At the present time, these different clones should be regarded as true species homologues of the histamine H_1-receptor, even though there are notable differences between them in some antagonist potencies (table 4). Unfortunately, the number of H_1-receptor antagonists evaluated in binding studies in cells transfected with the different recombinant receptors is rather limited. Nevertheless, it is clear that the stereoisomers of chlorpheniramine show marked differences between species. For example, the guinea pig H_1-receptor has a K_D of 0.9 nM for (+)-chlorpheniramine, whereas for the rat H_1-receptor, the value is nearer 8 nM (table 4). Similar differences for this compound and others (notably mepyramine and triprolidine) have been reported for the native H_1-receptors in guinea pig and rat brain, respectively (table 4; Chang et al., 1979b; Hill and Young, 1980; Hill, 1990). Such species differences may also explain why [^{125}I]iodobolpyramine can label guinea pig CNS H_1-receptors but is unable to detect H_1-receptors in rat brain (Körner et al., 1986; Bouthenet et al., 1988). The native H_1-receptor protein has been solubilized from both guinea pig and rat brain membranes (Toll and Snyder, 1982; Treherne and Young, 1988a), and the solubilized receptor retains the same differences in H_1-antagonist potency for (+)-chlorpheniramine as that observed in membranes (Toll and Snyder, 1982). What is not clear, however, is why mepyramine appears to be more potent as an antagonist of the recombinant rat H_1-receptor (expressed in C6 cells) than it is of the native H_1-receptor in rat brain membranes (table 4; Chang et al., 1979b; Hill and Young, 1980; Fujimoto et al., 1993). The recombinant study performed in rat C6 cells (Fujimoto et al., 1993) is complicated by the presence of a low level of endogenous H_1-receptors (Peakman and Hill, 1994), but a high affinity for mepyramine (K_D = 1 nM) has been deduced from functional studies in untransfected C6 cells (table 4; Peakman and Hill, 1994).

Site-directed mutagenesis has begun to shed some light on the binding domains for H_1-agonists and -antagonists. Amino acid sequence alignment of the cloned histamine H_1- and H_2-receptors (see fig. 5) has led to the suggestion that the third (TM3) and fifth (TM5) transmembrane domains of the receptor proteins are responsible for binding histamine (Birdsall, 1991; Timmerman, 1992a). Aspartate (107) in TM3 of the human H_1-receptor, which is conserved in all aminergic receptors, has

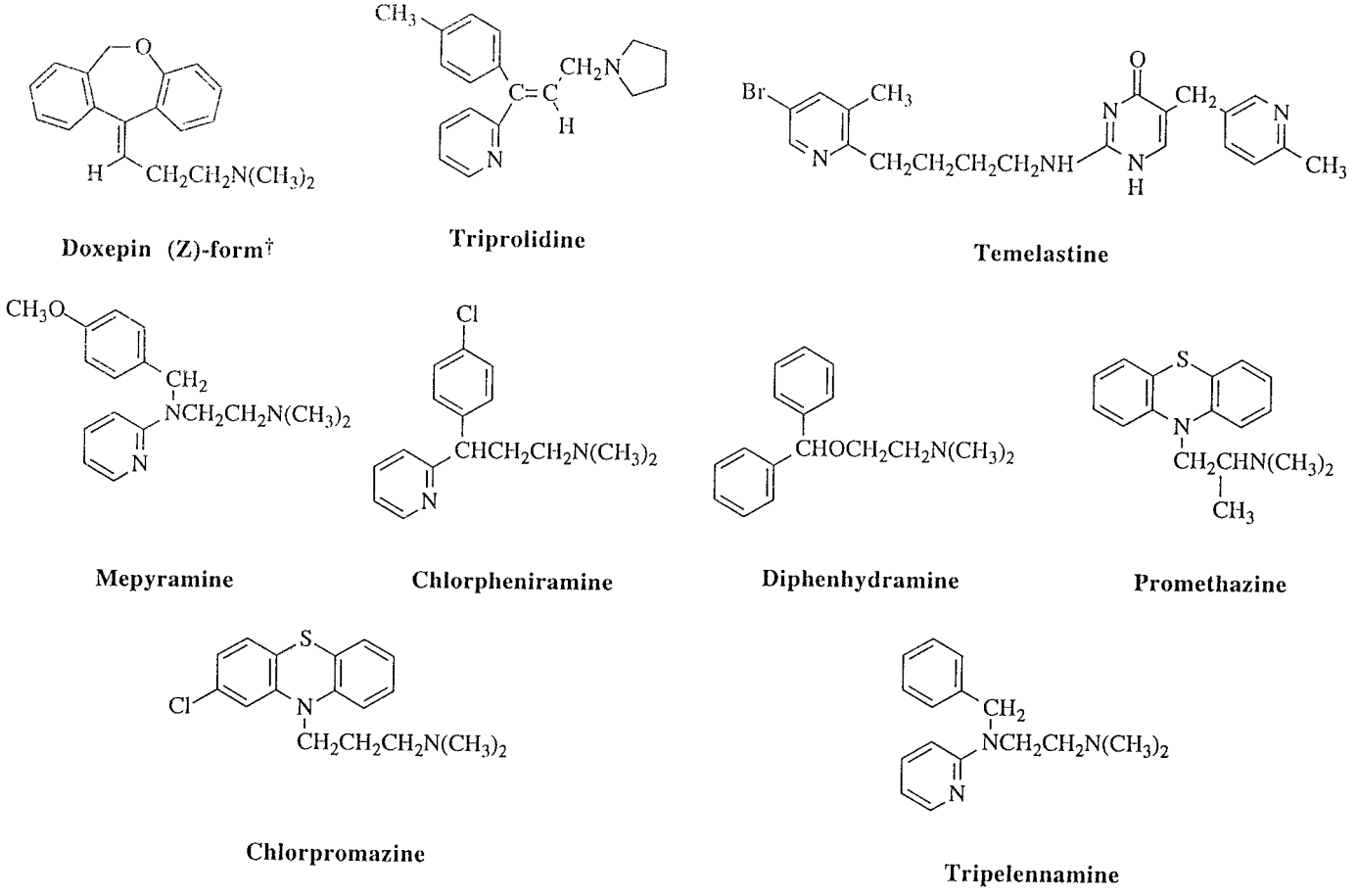

FIG. 3. Histamine H_1-receptor antagonists.

TABLE 4

Species variation in H_1-receptor antagonist potency (K_i, nM)

Antagonist	Guinea pig		Human		Rat		Bovine	
	h_1[a] (CHO)	H_1[b] (brain)	h_1 (CHO)	H_1 (brain)	h_1 (C6)	H_1 (brain)	h_1 (COS-7)	H1 (Adrenal Medulla)
Mepyramine	0.7	0.8	1.1, 4.0	1.0	1.7 (1.0)[c]	9.1	2.6	0.9
(+)-Chlorpheniramine	0.9	0.8	3.5, 2.5	4.2	7.5 (4.4)[c]	9.1	8.0	4.4
(−)-Chlorpheniramine	103	200	316	350	540 (>620)[c]	500	760	350
Triprolidine	0.7	0.2	1.0	3.7	2.0	5.6	n.d.	0.8

Unless otherwise stated, values show K_i determinations from inhibition of [^{3}H]mepyramine binding. n.d., not determined.

[a] h_1 = transfected H_1-receptor cDNA.

[b] H_1 = native/endogenous H_1-receptor.

[c] Values in parentheses show the values obtained from functional studies of the endogenous H_1-receptor present in rat C6 cells (Peakman & Hill, 1994).

been shown to be essential for the binding of histamine and H_1-receptor antagonists to the H_1-receptor (Ohta et al., 1994). In the α_2- and β_2-adrenoceptors, two serine residues in TM5 accept the phenolic hydroxyl groups of the catechol ring of noradrenaline. In the H_1-receptor, the residues corresponding to asparagine (198) and threonine (194) are in corresponding positions in TM5 of the human H_1-receptor. However, substitution of an alanine for threonine (194) did not influence either agonist or antagonist binding (Ohta et al., 1994; Moguilevsky et al., 1995). Substitution of alanine (198) for asparagine (198) substantially decreased agonist, but not antagonist affinity (Ohta et al., 1994; Moguilevsky et al., 1995). Similar mutations to the corresponding residues (threonine (203) and asparagine (207) in the guinea pig H_1-receptor sequence produce very similar results (Leurs et al., 1994a). It is interesting to note, however, that whereas 2-methylhistamine is similarly affected by the asparagine[207] alanine mutation, the H_1-selective agonists 2-thiazolylethylamine, 2-pyridylethylamine, and 2-(3-bromophenyl)histamine are much less affected by this mutation (Leurs et al., 1994a). These data suggest

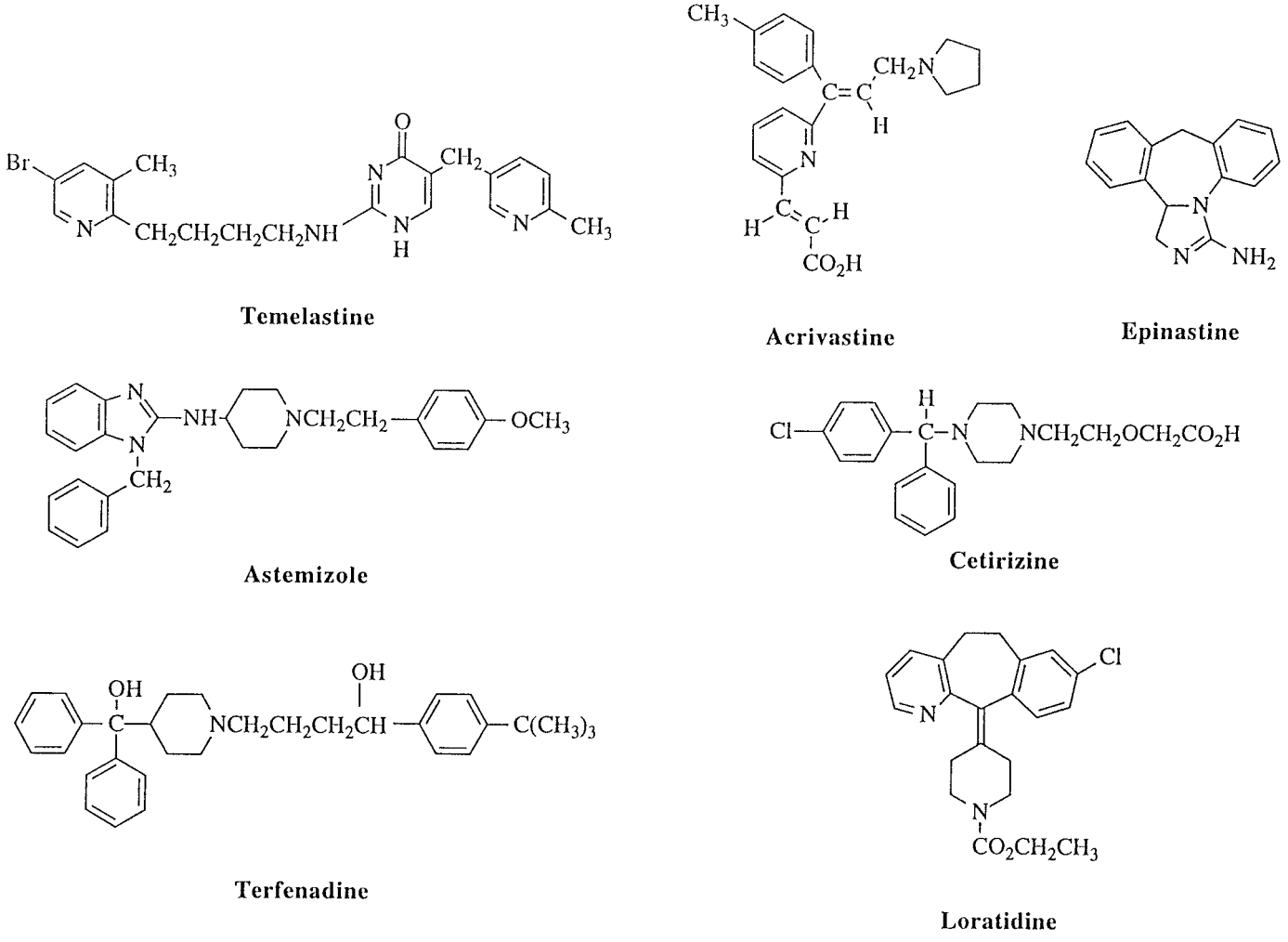

FIG. 4. "Nonsedating" H_1-receptor antagonists. †, The pharmaceutical product may be a mix of (E) and (Z) forms.

TABLE 5
"Nonsedating" H_1-receptor antagonists

Agent	pK_i value	Reference
Temelastine	9.5	Ter Laak et al. (1993)
Acrivastine	9.2	Leurs et al. (1995b)
Epinastine	8.9	Ter Laak et al. (1994)
Astemizole	8.3	Ter Laak et al. (1993)
Cetirizine	7.5	Ter Laak et al. (1993)
Terfenadine	7.1	Ter Laak et al. (1993)
Loratidine	6.8	Ter Laak et al. (1993)

Values are pK_i (−log dissociation constant) determined from inhibition of [^{3}H]mepyramine binding in homogenates of guinea pig cerebellum.

that asparagine (207) interacts with the N^{τ}-nitrogen of the imidazole ring of histamine. Furthermore, Leurs et al. (1995a) have recently shown that lysine (200) interacts with the N^{π}-nitrogen of histamine and is important for the activation of the H_1-receptor by histamine and the nonimidazole agonist, 2-pyridylethylamine. Interestingly, however, the lysine (200) alanine mutation did not alter the binding affinity of 2-pyridylethylamine to the guinea pig H_1-receptor (Leurs et al., 1995).

D. Signal Transduction Mechanisms

The primary mechanism by which histamine H_1-receptors produce functional responses in cells is the activation of phospholipase C via a pertussis toxin-insensitive G-protein that is probably related to the $G_{q/11}$ family of G-proteins (Hill, 1990; Leurs et al., 1995b). The number of tissues and cell types in which a histamine H_1-receptor–mediated increase in either inositol phosphate accumulation or intracellular calcium mobilization has been described is extensive, and further details are provided in several comprehensive reviews (Hill, 1990; Hill and Donaldson, 1992; Leurs et al., 1995b). Stimulation by histamine of [^{3}H]inositol phosphate accumulation and calcium mobilization has also been observed in Chinese hamster ovary (CHO) cells transfected with the human, bovine, and guinea pig H_1-receptor complementary deoxyribonucleic acid (cDNA) (Leurs et al., 1994c; Smit et al., 1996c; Iredale et al., 1993; Megson et al., 1995). It is worth noting, however, that in some tissues, histamine can stimulate inositol phospholipid hydrolysis independently of H_1-receptors. Thus, in the longitudinal smooth muscle of guinea pig ileum and neonatal

TABLE 6
Comparison of recombinant histamine receptors

Receptor	Species	Tissue of origin	Amino acid residues	Calculated mean weight (kDa)	Accession number	% Homology to human
H_1-receptor	Human	Genomic[a]	487	55.7	P35367	100
	Bovine	Adrenal medulla[b]	491	55.9	P30546	89.9
	Rat	Genomic[c]	486	55.6	P31390	87.8
	Guinea pig	Genomic[d]	488	55.6	P31389	82.9
	Mouse	Genomic[i]	489	55.6	D50095	84.0
H_2-receptor	Human	Genomic[e]	359	40.1	P25021	100
	Canine	Genomic[f]	359	40.2	P17124	92.5
	Rat	Genomic[g]	358	40.2	P25102	91.1
	Guinea pig	Liver[h]	359	40.5	JC4120	93.3
	Mouse	Genomic[j]	359	40.4	D50096	91.1

[a] De Backer et al. (1993)
[b] Yamashita et al. (1991b)
[c] Fujimoto et al. (1993)
[d] Horio et al. (1993)
[e] Gantz et al. (1991b)
[f] Gantz et al. (1991a)
[g] Ruat et al. (1991)
[h] Traiffort et al. (1995)
[i] Inove et al. (1996)
[j] Kobayashi et al. (1996)

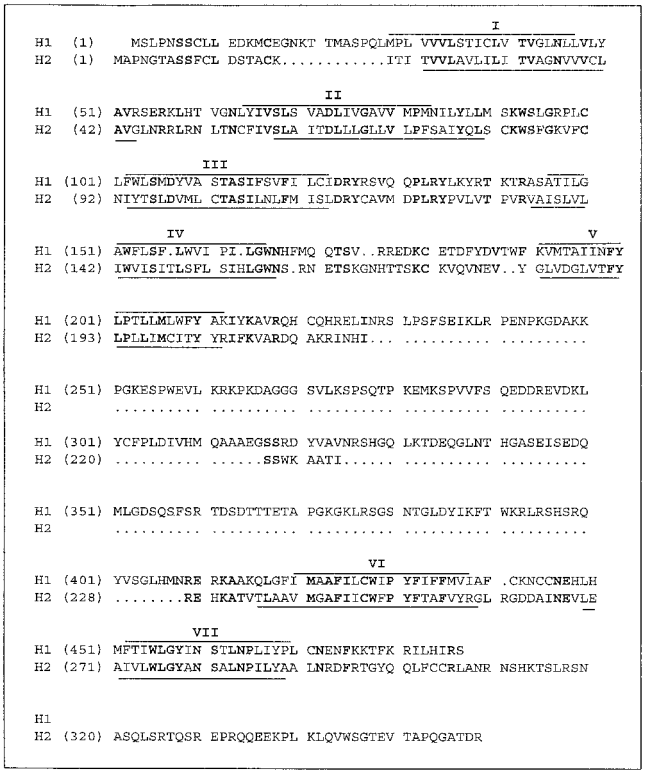

FIG. 5. Alignment of amino acid sequences of the human histamine H_1- and H_2-receptors. Residues that are identical in the two sequences are shown in bold. Lines show the putative transmembrane spanning domains.

rat brain (Donaldson and Hill, 1985, 1986b; Claro et al., 1987), a component can be identified in the response to histamine that is resistant to inhibition by H_1-receptor antagonists. It remains to be established, however, whether these effects are due to "tyramine-like" effects of histamine on neurotransmitter release (Bailey et al., 1987; Young et al., 1988a) or direct effects of histamine on the associated G-proteins (Seifert et al., 1994).

In addition to effects on the inositol phospholipid signaling systems, histamine H_1-receptor activation can lead to activation of several other signaling pathways, many of which appear to be secondary to changes in intracellular calcium concentration or the activation of protein kinase C. Thus, histamine can stimulate nitric oxide synthase activity (via a Ca^{2+}/calmodulin-dependent pathway) and subsequent activation of soluble guanylyl cyclase in a variety of different cell types (Schmidt et al., 1990; Leurs et al., 1991a; Yuan et al., 1993; Casale et al., 1985; Duncan et al., 1980; Hattori et al., 1990; Sertl et al., 1987). Arachidonic acid release and the synthesis of arachidonic acid metabolites such as prostacyclin and thromboxane A_2 can also be enhanced by H_1-receptor stimulation (Carter et al., 1988; Resink et al., 1987; Leurs et al., 1994c; Muriyama et al., 1990). Interestingly, in CHO-K1 cells transfected with the guinea pig H_1-receptor, the histamine-stimulated release of arachidonic acid is partially inhibited (approximately 40%) by pertussis toxin, whereas the same response in HeLa cells possessing a native H_1-receptor was resistant to pertussis toxin treatment (Leurs et al., 1994c). The reason for this difference remains to be established, but it does caution against the use of signal transduction pathways in highly expressed recombinant cell systems as a primary receptor classification tool. This point is best illustrated by the fact that in intact cellular systems, H_1-receptor activation can produce substantial changes in the intracellular levels of cAMP. In most tissues, histamine H_1-receptor activation does not activate adenylyl cyclase directly but acts to amplify direct cAMP responses to histamine H_2-, adenosine A_2-, and vasoactive intestinal polypeptide receptors (Palacios et al., 1978; Al-Gadi and Hill, 1987, 1985; Donaldson et al., 1989; Garbarg and Schwartz, 1988; Magistretti and Schorderet, 1985; Marley et al., 1991). In many of these cases, a role for both intracellular Ca^{2+} ions and protein kinase C has been implicated in this augmentation response (Al-Gadi and Hill, 1987; Schwabe et al., 1978; Garbarg and Schwartz, 1988). In CHO cells transfected with the bovine or guinea pig H_1-receptor, H_1-

receptor activation can also lead to both direct cAMP responses and to an enhancement of forskolin-stimulated cAMP formation (Leurs et al., 1994c; Sanderson et al., 1996).

III. Histamine H_2-Receptor

A. Distribution and Function

Unlike the situation with H_1-selective radioligands, attempts to map the distribution of H_2-receptors by using radiolabeled H_2-receptor antagonists have met with variable success (Hill, 1990). Thus, [^{3}H]cimetidine and [^{3}H]ranitidine have proved unsuitable as H_2-radioligands, and in the case of cimetidine, the binding to sites specifically labeled with the radioligand is potently inhibited by imidazoles that have very low H_2-receptor binding affinities (Burkard, 1978; Kendall et al., 1980; Smith et al., 1980; Bristow et al., 1981; Warrender et al., 1983). More success has been achieved with [^{3}H]tiotidine, which has a higher affinity for the H_2-receptor (table 7) in guinea pig brain, lung parenchyma, and CHO-K1 cells transfected with the human H_2-receptor cDNA (Gajtkowski et al., 1983; Norris et al., 1984; Sterk et al., 1986; Foreman et al., 1985a; Gantz et al., 1991a), although studies in rat brain were not successful (Maayani et al., 1982). At the present time, [^{125}I]iodoaminopotentidine is the most successful H_2-radioligand (Hirschfeld et al., 1992). It has high affinity (K_D = 0.3 nM) for the histamine H_2-receptor in brain membranes (Martinez-Mir et al., 1990; Ruat et al., 1990b; Traiffort et al., 1992a) and CHO-K1 cells expressing the cloned rat H_2-receptor (Traiffort et al., 1992b). The compound has also been used for autoradiographic mapping of H_2-receptors in mammalian brain (Ruat et al., 1990a; Traiffort et al., 1992a). In human brain, histamine H_2-receptors are widely distributed with highest densities (measured using [^{125}I]iodoaminopotentidine) in the basal ganglia, hippocampus, amygdala, and cerebral cortex (Traiffort et al., 1992a). Lowest densities were detected in cerebellum and hypothalamus (Traiffort et al., 1992a). A similar distribution has been observed in guinea pig brain (Ruat et al., 1990b). [^{125}I]Iodoazidopotentidine has successfully been used for irreversible labeling (Ruat et al., 1990b; Hirschfeld et al., 1992).

Most information to date on the distribution of histamine H_2-receptor, however, has been provided by functional studies in different tissues (Hill, 1990). Histamine H_2-receptor–stimulated cAMP accumulation or adenylyl cyclase activity has been demonstrated in a variety of tissues including brain (Hegstrand et al., 1976; Green et al., 1977; Kanof et al., 1977; Palacios et al., 1978; Gajtkowski et al., 1983; Al-Gadi and Hill, 1985, 1987), gastric cells (Soll and Wollin, 1979; Gespach et al., 1982), and cardiac tissue (Johnson et al., 1979a,b; Kanof and Greengard, 1979a; Johnson, 1982). Histamine H_2-receptors have a potent effect on gastric acid secretion, and the inhibition of this secretory process by H_2-receptor antagonists has provided evidence for an important physiological role of histamine in the regulation of gastric secretion (Black et al., 1972; Black and Shankley, 1985; Soll and Berglindh, 1987). High concentrations of histamine are also present in cardiac tissues of most animal species and can mediate positive chronotropic and inotropic effects on atrial or ventricular tissues via H_2-receptor stimulation (Black et al., 1972; Inui and Imamura, 1976; Levi et al., 1982; Hattori et al., 1983; Hattori and Levi, 1984; Hescheler et al., 1987; Levi and Alloatti, 1988). H_2-receptor–mediated smooth muscle relaxation has also been documented in airway, uterine, and vascular smooth muscle (Black et al., 1972; Reinhardt and Ritter, 1979; Gross et al., 1981; Eyre and Chand, 1982; Edvinsson et al., 1983; Foreman et al., 1985b; Ottosson et al., 1989). Finally, histamine H_2-receptors can inhibit a variety of functions within the immune system (Hill, 1990). H_2-receptors on basophils

TABLE 7
Histamine receptor radioligands

Receptor	Ligand	K_D	Tissue
H_1-receptor	[^{3}H]Mepyramine	0.8 nM	Guinea pig brain[a]
	[^{125}I]Iodobolpyramine	0.1 nM	Guinea pig brain[b]
	[^{125}I]Iodoazidophenpyramine	0.01 nM	Guinea pig cerebellum[c]
	[^{11}C]Mepyramine	1.0 nM	Human brain (in vivo)[d]
	[^{11}C]Doxepin	0.1 nM	Human brain (in vivo)[e]
H_2-receptor	[^{3}H]Tiotidine	25 nM	Guinea pig brain[f]
	[^{125}I]Iodoaminopotentidine	0.3 nM	Guinea pig brain[g]
	[^{125}I]Iodoazidopotentidine	10 nM	Guinea pig brain[g]
H_3-receptor	[^{3}H]R-(α)-methylhistamine	0.5 nM	Rat brain[h]
	[^{3}H]N$^\alpha$-methylhistamine	2.0 nM	Rat cerebral cortex[i]
	[^{125}I]Iodophenpropit	0.3 nM	Rat cerebral cortex[j]
	[^{125}I]Iodoproxyfan	0.065 nM	Rat striatum[k]
	[^{3}H]GR168320	0.1 nM	Rat cerebral cortex[l]

[a] Hill et al. (1981)
[b] Körner et al. (1986)
[c] Ruat et al. (1988)
[d] Villemagne et al. (1991)
[e] Yanai et al. (1995)
[f] Gajtkowski et al. (1983)
[g] Ruat et al. (1990a)
[h] Arrang et al. (1990)
[i] Clark and Hill (1995)
[j] Jansen et al. (1992)
[k] Ligneau et al. (1994)
[l] Brown et al. (1994)

and mast cells have been shown to negatively regulate the release of histamine (Bourne et al., 1971; Lichtenstein and Gillespie, 1975; Lett-Brown and Leonard, 1977; Ting et al., 1980; Plaut and Lichtenstein, 1982). Furthermore, there is increasing evidence that H_2-receptors on lymphocytes can inhibit antibody synthesis, T-cell proliferation, cell-mediated cytolysis, and cytokine production (Bourne et al., 1971; Melmon et al., 1974, 1981; Griswold et al., 1984; Khan et al., 1985, 1986; Sansoni et al., 1985; Melmon and Khan, 1987). In the CNS, histamine H_2-receptor activation can inhibit nerve cells (Haas and Bucher, 1975; Haas and Wolf, 1977), but the most intriguing action is a block of the long-lasting after-hyperpolarization and the accommodation of firing, an effect with a remarkably long duration leading to potentiation of excitation in rodents (Haas and Konnerth, 1983; Haas and Greene, 1986) and human brain (Haas et al., 1988). A slow excitation is also common (Greene and Haas, 1989; Phelan et al., 1990). Synaptic transmission in the hippocampus is profoundly enhanced (Kostopoulos et al., 1988), and synaptic plasticity is induced or enhanced (Brown et al., 1995). An increase of the hyperpolarization-activated current has also been described in thalamic relay neurons (McCormick and Williamson, 1991). Indications for non-cAMP mediated actions of H_2-receptor activation are given by Haas et al. (1978) and Jahn et al. (1995).

B. H_2-Selective Ligands

The initial definition of the H_1- and H_2-subclasses of histamine receptor by Ash and Schild (1966) and Black and colleagues (1972) led to a successful search for H_2-receptor selective antagonists with clinical relevance for the treatment of peptic ulcer. Burimamide was the first compound developed that showed selectivity for the H_2-receptor (Black et al., 1972), but more recent work has shown that this compound is a more potent H_3-receptor antagonist (Arrang et al., 1983). Cimetidine and metiamide were developed directly from burimamide (Black et al., 1974; Brimblecombe et al., 1975; Ganellin, 1978). Since then, a large number of compounds have been developed with H_2-receptor antagonist properties [see Ganellin (1992) for review]. These include ranitidine (Bradshaw et al., 1979), tiotidine (Yellin et al., 1979), nizatidine (Lin et al., 1986), famotidine (Takeda et al., 1982), and mifentidine (Donetti et al., 1984), which have been extensively used for characterization purposes (table 3; fig. 6). Iodoaminopotentidine (K_D = 2.5 nM) is one of the most potent H_2-receptor antagonists available, and, as mentioned above, this compound has been used as a successful radioligand (Hirschfeld et al., 1992). Most H_2-receptor antagonists are polar compounds and penetrate poorly into the CNS. Although this property is of great use for selective actions on peripheral tissues (e.g., gastric mucosa), it does limit the use of the com-

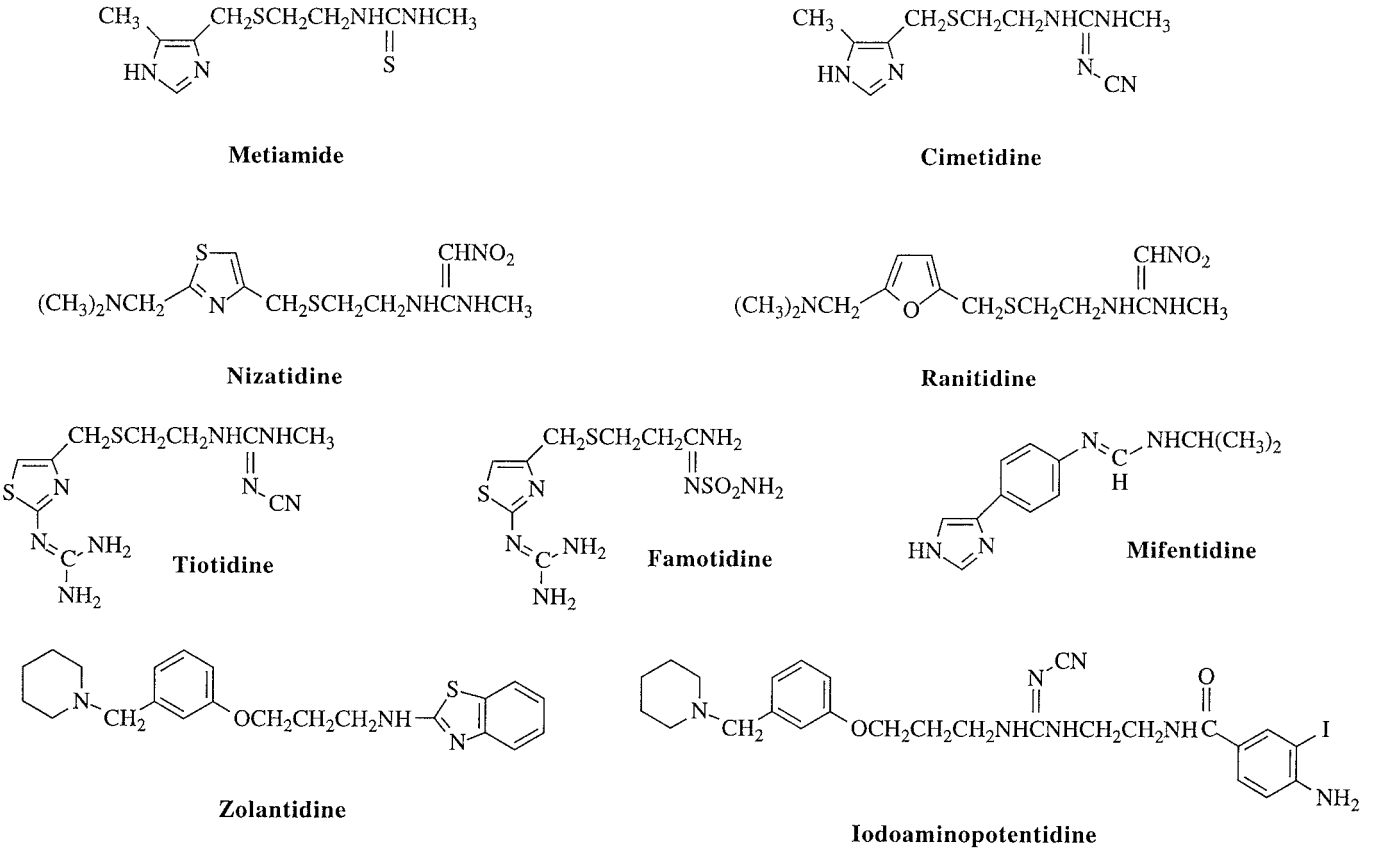

FIG. 6. Histamine H_2-receptor antagonists.

pounds for the in vivo evaluation of H_2-receptor function within the CNS. However, one compound (zolantidine) is a potent and selective brain-penetrating histamine H_2-receptor antagonist (table 3; Calcutt et al., 1988; Young et al., 1988b). Both cimetidine and ranitidine have been shown to demonstrate inverse agonism on histamine H_2-receptors transfected into CHO cells (Smit et al., 1996a). Thus, in CHO cells expressing high levels of H_2-receptors, in which a considerable constitutive activation of H_2-receptors was demonstrated, cimetidine and ranitidine inhibited basal adenylyl cyclase activity (Smit et al., 1996a). In contrast, burimamide behaved as a neutral antagonist (Smit et al., 1996a).

4-Methylhistamine was the first agonist described that had any selectivity for the H_2-receptor (Black et al., 1972), although more potent and selective H_2-agonists are now available (table 2). It is noteworthy that many of the selective H_2-agonists exhibit H_1- or H_3-antagonist properties (see table 2); consequently the demonstration of H_2-agonism in a given tissue or cell type needs confirming with H_2-antagonists. Impromidine is approximately 48 times more potent than histamine in mediating atrial chronotropic responses, but in several other H_2-receptor–containing tissues, its relative potency and efficacy are lower (Durant et al., 1978; Leurs et al., 1995b). A large number of impromidine analogues have been synthesized and evaluated for H_2-agonism. These studies have led to the development of the potent H_2-agonists, sopromidine and arpromidine (table 2; Timmerman, 1992c). Arpromidine and analogues are potential candidates for treatment of congestive heart failure (Buschauer, 1989; Buschauer and Baumann, 1991; Mörsdorf et al., 1990). Another potent H_2-agonist has been derived as an analogue of dimaprit by considering cyclic forms of the isothiourea group (Eriks et al., 1992).

C. Receptor Structure

Photoaffinity binding studies using [^{125}I]iodoazidopotentidine and sodium dodecyl sulfate-polyacrylamide gel electrophoresis have suggested that the H_2-receptor in guinea pig hippocampus and striatum has a molecular weight of 59 kDa (Ruat et al., 1990b). However, comparison with the calculated molecular weights (40.2 to 40.5 kDa) for the recently cloned H_2-receptors (table 6) suggests that the native H_2-receptor in guinea pig brain is glycosylated. Consistent with this proposal, it is noteworthy that all of the cloned H_2-receptor proteins possess N-glycosylation sites in the N-terminus region (Gantz et al., 1991a,b; Ruat et al., 1991; Traiffort et al., 1995). Removal of these glycosylation sites by site-directed mutagenesis, however, has shown that N-glycosylation of the H_2-receptor is not essential for cell surface localization, ligand binding, or coupling via G_s to adenylyl cyclase (Fukushima et al., 1995).

The H_2-receptor was first cloned by Gantz and colleagues using the polymerase chain reaction to amplify a partial length H_2-receptor sequence from canine gastric parietal cDNA using degenerate oligonucleotide primers (Gantz et al., 1991b). This sequence was then used to identify a full length H_2-receptor clone following screening of a canine genomic library (Gantz et al., 1991b). Rapid cloning of the rat, human, guinea pig, and mouse H_2-receptors followed (Gantz et al., 1991a; Ruat et al., 1991; Traiffort et al., 1995; Kobayashi et al., 1996). These DNA sequences encode for a 359 (canine, human, guinea pig) or 358 (rat) receptor protein that has the general characteristics of a G-protein-coupled receptor. The most notable difference between the structure of the cloned H_2- and H_1- receptors is the much shorter 3rd intracellular loop of the H_2-receptor and the longer H_2-receptor C terminus. Expression of the rat and human H_2-receptor proteins in CHO cells has revealed the expected pharmacological specificity of H_2-receptors as judged by radioligand binding studies using [^{125}I]iodoaminopotentidine (Traiffort et al., 1992b; Leurs et al., 1994c). Recent chromosomal mapping studies have assigned the H_2-receptor gene to human chromosome 5 (Traiffort et al., 1995).

Comparison of the H_2-receptor sequence with other biogenic amine G-protein–coupled receptors has indicated that an aspartate in TM3 and an aspartate and threonine residue in TM5 are responsible for binding histamine (Birdsall, 1991). Replacement of aspartate (98) by an asparagine residue in the canine H_2-receptor results in a receptor that does not bind the antagonist tiotidine and does not stimulate cAMP accumulation in response to histamine (Gantz et al., 1992). Similarly, changing the aspirate (186) of TM5 to an alanine resulted in complete loss of tiotidine binding without affecting the EC_{50} for histamine-stimulated cAMP formation (Gantz et al., 1992). Changing the threonine (190) to an alanine, however, resulted in a lower K_D for tiotidine and a reduction in both the maximal cAMP response and histamine EC_{50} value (Gantz et al., 1992). Mutation of Asp (186) and Gly (187) in the canine H_2-receptor (to Ala (186) and Ser (187), however, produces a bifunctional receptor that can be stimulated by adrenaline and inhibited by both propranolol and cimetidine (Delvalle et al., 1995). Thus, these data suggest that the pharmacological specificity of the H_2-receptor resides in only a few key amino acid residues.

Other site-directed mutagenesis studies on the H_2-receptor have been very limited. However, Smit et al. (1996) have identified a residue in the second intracellular loop [leucine (124)] of the rat H_2-receptor, which appears necessary for efficient coupling to G_s.

D. Signal Transduction Mechanisms

It is generally accepted that histamine H_2-receptors couple to adenylyl cyclase via the GTP-binding protein G_s (Johnson, 1982; Hill, 1990; Leurs et al., 1995b). Histamine is a potent stimulant of cAMP accumulation in many cell types (Johnson, 1982), particularly those of CNS origin (Daly, 1977). Thus, H_2-receptor–mediated effects on cAMP accumulation have been observed in

brain slices (Al-Gadi and Hill, 1985; Palacios et al., 1978), gastric mucosa (Soll and Wollin, 1979; Chew et al., 1980; Batzri et al., 1982; Gespach et al., 1982), fat cells (Grund et al., 1975; Keller et al., 1981), cardiac myocytes (Warbanow and Wollenberger, 1979), vascular smooth muscle (Reinhardt and Ritter, 1979), basophils (Lichtenstein and Gillespie, 1975), and neutrophils (Busse and Sosman, 1977). Furthermore, H_2-receptor–mediated cAMP accumulation has been demonstrated in CHO cells transfected with the rat, canine, or human H_2-receptor cDNA (Gantz et al., 1991a,b; Leurs et al., 1994b; Fukushima et al., 1995).

Direct stimulation of adenylyl cyclase activity in cell-free preparations has been detected in both brain and cardiac muscle membranes (Hegstrand et al., 1976; Green et al., 1977; Green and Maayani, 1977; Kanof et al., 1977; Johnson et al., 1979a,b; Kanof and Greengard, 1979a,b; Newton et al., 1982; Olianas et al., 1984). However, caution is required regarding the interpretation of receptor characterization studies using histamine-stimulated adenylyl cyclase activity alone (Hill, 1990). A striking feature of studies of histamine H_2-receptor–stimulated adenylyl cyclase activity in membrane preparations is the potent antagonism observed with certain neuroleptics and antidepressants (table 8; Spiker et al., 1976; Green et al., 1977; Green and Maayani, 1977; Kanof and Greengard, 1978; Green, 1983). It is notable, however, that most of the neuroleptics and antidepressants are approximately 2 orders of magnitude weaker as antagonists of histamine-stimulated cAMP accumulation in intact cellular systems (table 8; Tuong et al., 1980; Kamba and Richelson, 1983; Hill, 1990). One potential explanation of these differences resides within the buffer systems used for the cell-free adenylyl cyclase assays. Some differences in potency of some antidepressants and neuroleptics have been observed when membrane binding of H_2-receptors has been evaluated using [^{125}I]iodoaminopotentidine (table 8; Traiffort et al., 1991). However, invariably the differences observed in the K_i values deduced from ligand binding studies in different buffers are not as large as the differences in K_B values obtained from functional studies (table 8). For example, in the case of amitriptyline, no difference was observed in binding affinity in Krebs and Tris buffers (Traiffort et al., 1991).

In addition to G_s-coupling to adenylyl cyclase, there are reports of H_2-receptors coupling to other signaling systems. For example, in gastric parietal cells, H_2-receptor stimulation has been shown to increase the intracellular free concentration of calcium ions (Chew, 1985, 1986; Chew and Petropoulos, 1991; Malinowska et al., 1988; Delvalle et al., 1992a). A similar calcium response to histamine H_2-receptor stimulation has also been observed in HL-60 cells (Mitsuhashi et al., 1989; Seifert et al., 1992) and in hepatoma-derived cells transfected with the canine H_2-receptor cDNA (Delvalle et al., 1992b). In these latter cells, the influence on $[Ca^{2+}]_i$ was accompanied by both an increase in inositol trisphosphate accumulation and a stimulation of cAMP accumulation (Delvalle et al., 1992b). Interestingly, the H_2-receptor–stimulated calcium and inositol trisphosphate responses in these cells were both inhibited by cholera toxin treatment (but not by pertussis toxin), whereas cholera toxin produced the expected increase in cAMP levels (Delvalle et al., 1992a,b). In single parietal cells, H_2-receptors have been shown to release calcium from intracellular calcium stores (Negulescu and Machen, 1988). It should be noted, however, that no effect of H_2-agonists was observed on inositol phosphate accumulation or intracellular calcium levels in CHO cells transfected with the human H_2-receptor (Leurs et al., 1994a).

TABLE 8

Comparison of antagonist K_B values for inhibition of H_2-receptor-stimulated adenylyl cyclase activity in membranes and cyclic AMP accumulation in intact cellular systems

Antagonist	Antagonist K_B value (μM)			Binding studies (K_i, μM)	
	Slices[a]	Dissociated cells[b]	Homogenates[c,d,e]	Krebs buffer	Tris buffer
Cimetidine	0.6	0.5	0.9		
Metiamide	0.8	n.d.	1.0		
Tiotidine	n.d.	0.03	0.03	0.02	0.007
Cyproheptadine	5.7	n.d.	0.04		
Mianserin	10.0	2.8	0.07	1.01	0.20
Imipramine	>10	3.3	0.2		
Amitriptyline	3.5	1.9	0.05	0.09	0.09
Chlorpromazine	5.9	3.0	0.04		
Haloperidol	>10	29	0.08	1.61	0.42

Measurements were made of H_2-mediated adenylyl cyclase activity in homogenates of guinea pig hippocampus, impromidine-stimulated cyclic AMP accumulation in guinea pig hippocampal slices, and of H_2-mediated cyclic AMP accumulation in dissociated hippocampal tissue. n.d., not determined.

[a] Tuong et al. (1980)
[b] Kamba et al. (1983)
[c] Green et al. (1977)
[d] Kanof and Greengard (1978)
[e] Kanof and Greengard (1979a,b)
[f] Traiffort et al. (1991)

Thus, the effect of H_2-receptor stimulation on intracellular calcium signaling may be very cell-specific.

In CHO cells transfected with the rat H_2-receptor, H_2-receptor stimulation produces both an increase in cAMP accumulation and an inhibition of P_{2u}-receptor–mediated arachidonic acid release (Traiffort et al., 1992b). Interestingly, however, the effect on phospholipase A_2 activity (i.e., arachidonic acid release) was not mimicked by forskolin, PGE_1, or 8-bromo-cAMP, suggesting a mechanism of activation that is independent of cAMP-mediated protein kinase A activity (Traiffort et al., 1992b). However, in CHO cells transfected with the human H_2-receptor, no inhibitory effects of H_2-receptor stimulation were observed on phospholipase A_2 activity (Leurs et al., 1994b). This observation suggests that these cAMP-independent effects might depend on the level of receptor expression or subtle differences between clonal cell lines.

IV. Histamine H_3-Receptor

A. Distribution and Function

The high apparent affinity of R-(α)-methylhistamine for the histamine H_3-receptor has enabled the use of this compound as a radiolabeled probe (Arrang et al., 1987). This compound has been successfully used to identify a single binding site in rat cerebral cortical membranes, which in phosphate buffer has the pharmacological characteristics of the H_3-receptor (Arrang et al., 1987, 1990). [^{3}H]R-(α)-methylhistamine binds with high affinity (K_D = 0.3 nM) to rat brain membranes, although the binding capacity is generally low (approximately 30 fmol/mg protein; (Arrang et al., 1987). Autoradiographic studies with [^{3}H]R-(α)-methylhistamine have demonstrated the presence of specific thioperamide-inhibitable binding in several rat brain regions, particularly cerebral cortex, striatum, hippocampus, olfactory nucleus, and the bed nuclei of the stria terminalis, which receive ascending histaminergic projections from the magnocellular nuclei of the posterior hypothalamus (Arrang et al., 1987; Pollard et al., 1993). H_3-receptors have also been visualized in human brain and the brain of nonhuman primates (Martinez-Mir et al., 1990). H_3-receptor binding has been additionally characterized using [^{3}H]R-(α)-methylhistamine in guinea pig cerebral cortical membranes (Kilpatrick and Michel, 1991), guinea pig lung (Arrang et al., 1987), guinea pig intestine, and guinea pig pancreas (Korte et al., 1990). N^α-methylhistamine has also proved successful as a radiolabeled probe for the H_3-receptor. Although the relative agonist activity of N^α-methylhistamine (with respect to histamine) is fairly similar for all three histamine receptor subtypes (table 2), the binding affinity of histamine and N^α-methylhistamine for the H_3-receptor is several orders of magnitude higher than for either the H_1- or H_2-receptors (Hill et al., 1977; Ruat et al., 1990b). This ligand can identify high-affinity H_3-receptor sites in both guinea pig (Korte et al., 1990) and rat (West et al., 1990; Kathman et al., 1993; Clark and Hill, 1995) brain.

The binding of ^{3}H-agonists to H_3-receptors in brain tissues has been shown to be regulated by guanine nucleotides, implying a linkage to heterotrimeric G-proteins (Arrang et al., 1987, 1990; Zweig et al., 1992; Clark and Hill, 1995). The binding of H_3-receptor agonists also seems to be sensitive to several cations. Magnesium and sodium ions have been shown to inhibit [^{3}H]R-(α)-methylhistamine binding in rat and guinea pig brain (Kilpatrick and Michel, 1991), and the presence of calcium ions has been reported to reveal heterogeneity of agonist binding (Arrang et al., 1990). The inhibitory effect of sodium ions on agonist binding means that higher B_{max} values are usually obtained in sodium-free Tris buffers compared with that in Na/K phosphate buffers (Clark and Hill, 1995). West et al. (1990) have suggested that multiple histamine H_3-receptor subtypes exist in rat brain (termed H_{3A} and H_{3B}) on the basis of [^{3}H]N^α-methylhistamine binding in rat cerebral cortical membranes in 50 mM Tris buffer. Under these conditions, the selective H_3-antagonist thioperamide can discriminate two affinity binding states (West et al., 1990). However, Clark and Hill (1995) have noted that the observed heterogeneity of thioperamide binding is dependent on the concentration of sodium ions or guanine nucleotides within the incubation medium. Thus, in the presence of 100 mM sodium chloride, thioperamide binding conforms to a single binding isotherm (Clark and Hill, 1995). The simplest interpretation of these data is that the H_3-receptor can exist in different conformations for which thioperamide, but not agonists or other H_3-antagonists (e.g., clobenpropit), can discriminate. Clark and Hill (1995) have suggested that the equilibrium between these conformations is altered by guanine nucleotides or sodium ions. If this hypothesis is correct, it is likely that the different binding sites represented resting, active, or G-protein–coupled conformations of the H_3-receptor. Furthermore, if thioperamide preferentially binds to uncoupled receptors, then this compound should exhibit negative efficacy in functional assays.

More recently, radiolabeled H_3-receptor antagonists have become available. The first compound to be developed was [^{125}I]iodophenpropit, which has been used to successfully label H_3-receptors in rat brain membranes (Jansen et al., 1992). Inhibition curves for thioperamide and iodophenpropit were consistent with interaction with a single binding site, but H_3-receptor agonists were able to discriminate high- [4 nM for R-(α)-methylhistamine] and low- [0.2 μM for R-(α)-methylhistamine] affinity binding sites (Jansen et al., 1992). More recently, [^{3}H]GR16820 (Brown et al., 1994) and [^{125}I]iodoproxyfan (Ligneau et al., 1994) have also proved useful as high-affinity radiolabeled H_3-antagonists. [^{125}I]iodoproxyfan (Stark et al., 1996a) is the most potent and selective ligand available at the present time with a K_D of 65 pM (Ligneau et al., 1994). In rat striatum, in the

presence of guanine nucleotides such as guanosine 5′*O*-(3-thiotriphosphate) (GTPγS), 40% of the binding sites exhibited a 40-fold lower affinity for H_3-agonists, providing further evidence for a potential linkage of H_3-receptors to G-proteins (Ligneau et al., 1994). [^{3}H]thioperamide and [^{3}H]5-methylthioperamide have also been used to label H_3-receptors in rat brain membranes (Alves-Rodrigues et al., 1996; Yanai et al., 1994). However, [^{3}H]thioperamide was shown to bind additionally to low-affinity, high-capacity, non H_3-receptor sites in this tissue (Alves-Rodrigues et al., 1996).

In addition to data obtained from ligand binding studies, evidence for the localization of histamine H_3-receptors has also come from functional studies, primarily involving inhibition of neurotransmitter release. The H_3-receptor was first characterized as an autoreceptor-regulating histamine synthesis and release from rat cerebral cortex, striatum, and hippocampus (Arrang et al., 1983, 1985b,c 1987a, 1988a,b). H_3-receptor–mediated inhibition of histamine release has also been observed in human cerebral cortex (Arrang et al., 1988a). Differences in the distribution of H_3-receptor binding sites and the levels of histidine decarboxylase (an index of histaminergic nerve terminals) suggested at an early stage that H_3-receptors were not confined to histamine-containing neurons within the mammalian CNS (Arrang et al., 1987; Van der Werf and Timmerman, 1989). This has been confirmed by the observations that H_3-receptors can regulate serotonergic (Schlicker et al., 1988), noradrenergic (Schlicker et al., 1989, 1992), cholinergic (Clapham and Kilpatrick, 1992), and dopaminergic (Schlicker et al., 1993) neurotransmitter release in mammalian brain. Histamine H_3-receptor activation inhibits the firing of the histamine-neurons in the posterior hypothalamus through a mechanism different from autoreceptor functions found on other aminergic nuclei, presumably a block of Ca^{2+}-current (Haas, 1992). Electrophysiological evidence for reduction of excitatory transmitter release (glutamate) has been presented by Brown and Reymann (unpublished data, 1996).

Inhibitory effects of H_3-receptor activation on neurotransmission have also been documented in the periphery. Thus, H_3-receptors have been identified regulating the release of sympathetic neurotransmitters in guinea pig mesenteric artery (Ishikawa and Sperelakis, 1987), human saphenous vein (Molderings et al., 1992), guinea pig atria (Endou et al., 1994; Imamura et al., 1994), and human heart (Imamura et al., 1995). Inhibition of parasympathetic nerve activity has also been observed in guinea pig ileum and human bronchi and trachealis (Trzeciakowski, 1987; Tamura et al., 1988; Ichinose et al., 1989; Ichinose and Barnes, 1989; Hew et al., 1990; Menkveld and Timmerman, 1990; Leurs et al., 1991a,b; Poli et al., 1991). An inhibitory effect of H_3-receptor stimulation on release of neuropeptides (tachykinins or calcitonin gene-related peptide) from sensory C fibers has been reported from airways (Ichinose et al., 1990), meninges (Matsubara et al., 1992), skin (Ohkubo and Shibata, 1995), and heart (Imamura et al., 1996). A modulation of acetylcholine, capsaicin, and substance P effects by histamine H_3-receptors in isolated perfused rabbit lungs has also been reported (Delaunois et al., 1995).

There is evidence that H_3-receptor stimulation can inhibit the release of neurotransmitters from nonadrenergic-noncholinergic nerves in guinea pig bronchioles (Burgaud and Oudart, 1994) and ileum (Taylor and Kilpatrick, 1992). Interestingly, in guinea pig ileum, the H_3-antagonists betahistine and phenylbutanoylhistamine were much less potent as inhibitors of H_3-mediated effects on nonadrenergic-noncholinergic transmission than they were as antagonists of histamine release in rat cerebral cortex (Taylor and Kilpatrick, 1992). A similar low potency has been observed for these two antagonists for antagonism of H_3-receptor–mediated [^{3}H]acetylcholine release from rat entorhinal cortex (Clapham and Kilpatrick, 1992) and antagonism of H_3-receptor–mediated 5-hydroxytryptamine (5-HT) release from porcine enterochromaffin cells (Schworer et al., 1994). These observations provide support for the possible existence of distinct H_3-receptor subtypes, but these responses need to be investigated further to exclude alternative explanations. For example, Arrang et al. (1995) have recently shown that phenylbutanoylhistamine can inhibit [^{3}H]acetylcholine release from rat entorhinal cortex slices and synaptosomes via a nonhistamine receptor mechanism. Thus, the potency of phenylbutanoylhistamine as an H_3-receptor antagonist in these preparations may be greatly underestimated because of the additional nonspecific properties of the drug (Arrang et al., 1995).

The observed inhibitory effect of H_3-receptor stimulation on 5-HT release from porcine enterochromaffin cells in strips of small intestine (Schworer et al., 1994) provides evidence for H_3-receptors regulating secretory mechanisms in nonneuronal cells. This observation suggests that H_3-receptors may also be present in gastric mast cells or enterochromaffin cells and exert an inhibitory influence on histamine release and gastric acid secretion. Consistent with this suggestion, H_3-receptor activation has been shown to inhibit gastric acid secretion in conscious dogs (Soldani et al., 1993). An autoregulation of histamine synthesis by histamine H_3-receptors has also been reported in isolated rabbit fundic mucosal cells (Hollande et al., 1993).

H_3-receptors have been shown to relax rabbit middle cerebral artery via an endothelium-dependent mechanism involving both nitric oxide and prostanoid release (Ea Kim and Oudart, 1988; Ea Kim et al., 1992). Finally, there is a report that H_3-receptor activation can stimulate adrenocorticotropic hormone release from the pituitary cell line AtT-20 (Clark et al., 1992)

B. H_3*-Receptor Selective Ligands*

The initial characterization of the H_3-receptor made use of the relative high affinity of the agonists N^{α}-methylhistamine and histamine for the H_3-receptor compared with the H_1- and H_2-receptors together with the H_3-antagonist properties of impromidine (H_2-agonist), burimamide (H_2-antagonist), and betahistine (H_1-agonist) (Arrang et al., 1983, 1985a). Since then, several selective ligands (both agonists and antagonists) have been developed that show little effect on H_1- and H_2-receptors. The first selective H_3-agonist was R-(α)-methylhistamine (fig. 2), which capitalized on the marked stereoselectivity of agonist binding to the H_3-receptor compared with that to the other histamine receptors (Arrang et al., 1985c). Thus, R-(α)-methylhistamine is two orders of magnitude more potent as an H_3-agonist than the corresponding S-isomer (table 2). R-α_1S-β-dimethylhistamine showed slightly higher potency and even higher selectivity (Lipp et al., 1992). Imetit [S-[2–4(5)-imidazolylethylisothiourea] is a highly selective, full H_3-agonist that appears to be more potent than R-(α)-methylhistamine (table 2; Garbarg et al., 1992; Howson et al., 1992; Van der Goot et al., 1992). Both R-(α)-methylhistamine and imetit have been shown to be active in vivo at low doses (Arrang et al., 1987a; Garbarg et al., 1992). Azomethine derivatives of R-(α)-methylhistamine were prepared as lipophilic prodrugs to improve the bioavailability of the hydrophilic drug, particularly its entry into the brain (Krause et al., 1995). Immepip is another potent H_3-agonist that has been developed from histamine by extending the alkyl side chain to four methylene groups and incorporating the amino function within a piperidine ring (table 2; Vollinga et al., 1994). Most recently, the H_3-agonist potency of a cyclic, conformationally restricted analogue of histamine (immepyr) has been reported (Shih et al., 1995). This compound has been resolved and the (+)-immepyr shown to have an H_3-binding affinity (K_i = 2.8 nM) one order of magnitude higher than the corresponding (-)-isomer (Shih et al., 1995). In guinea pig ileum, however, (+)-immepyr was one order of magnitude less potent (pD_2 7.1) than R-(α)-methylhistamine (pD_2 8.2) as an H_3-agonist (Shih et al., 1995).

Thioperamide was the first potent and selective H_3-receptor antagonist to be described (Arrang et al., 1987). This compound appears to act as a competitive antagonist in most functional assays of H_3-receptor activity (Arrang et al., 1987; Hew et al., 1990; Menkveld and Timmerman, 1990), although Clark and Hill (1995) have suggested that it may possess inverse agonist properties. More recently, several other potent H_3-antagonists have been described (table 3; fig. 7), including clobenpropit (Kathman et al., 1993), iodophenpropit (Jansen et al., 1992), GR175737 (Clitherow et al., 1996), iodoproxyfan (Ligneau et al., 1994; Schlicker et al., 1996), impentamine (Vollinga et al., 1995; Leurs et al., 1996), ethers (Ganellin et al., 1996; Stark et al., 1996a), and carbamates (Stark et al., 1996b). These compounds have initiated some further discussion regarding potential H_3-receptor subtypes. Thus, iodoproxyfan behaves as a partial agonist in both guinea pig ileum and mouse cerebral cortical slices, whereas its noniodinated analogue only exhibits slight agonist activity in the mouse brain preparation (Schlicker et al., 1996). In guinea pig ileum, the noniodinated analogue of iodoproxyfan is a pure antagonist (pA_2 7.12; Schlicker et al., 1996). These observations point to differences in receptor structure in the two preparations (perhaps species homologues?), but they could equally well be accommodated by differences in the efficiency of H_3-receptor–effector coupling between the two tissues. A similar observation has been made with a series of homologues of histamine in which the ethylene side chain was modified (Leurs et al., 1996). Lengthening the side chain of histamine from two to five methylene groups results in the highly selective H_3-antagonist impentamine, which is equipotent with thioperamide as a competitive antagonist in guinea pig jejunum (table 3; Vollinga et al., 1995). However, in mouse brain cerebral cortical slices, impentamine (like iodoproxyfan) exhibits partial agonist activity (Leurs et al., 1996). At the present time, differences in receptor-effector coupling (and hence H_3-receptor reserve) between mouse brain and guinea pig small intestine provide the simplest explanation for these observations.

Although many of the H_3-selective ligands have been fully characterized in terms of selectivity for each of the three histamine receptors, it is worth stressing that the evaluation of H_3-receptor ligands against other receptor systems is more limited. This needs to be borne in mind, particularly, when considering the in vivo use of these compounds. For example, iodophenpropit (K_i 11 nM) and thioperamide (K_i 120 nM) have both been shown to interact with 5-HT_3-receptors (Leurs et al., 1995c), whereas iodoproxyfan did not (Schlicker et al., 1995).

C. Receptor Structure

Structural information on the histamine H_3-receptor is very limited, primarily because of a lack of success in cloning the H_3-receptor cDNA. At the present time, there are only two reports of H_3-receptor purification studies. Using [^{3}H]histamine as a radioligand, Zweig et al. (1992) have reported the solubilization of an H_3-receptor protein from bovine whole brain. Size-exclusion chromatography has revealed an apparent molecular mass of 220 kDa (Zweig et al., 1992). However, because the solubilized receptor retained its guanine nucleotide sensitivity, it is likely that the molecular mass of 220 kDa represents a complex of receptor, G-protein, and digitonin (Zweig et al., 1992). Cherifi et al. (1992) have reported the solubilization (with Triton X-100) and purification of the H_3-receptor protein from the human gastric tumoral cell line HGT-1. After gel filtration and sepharose-thioperamide affinity chromatography, protein has been purified with a molecular mass of approx-

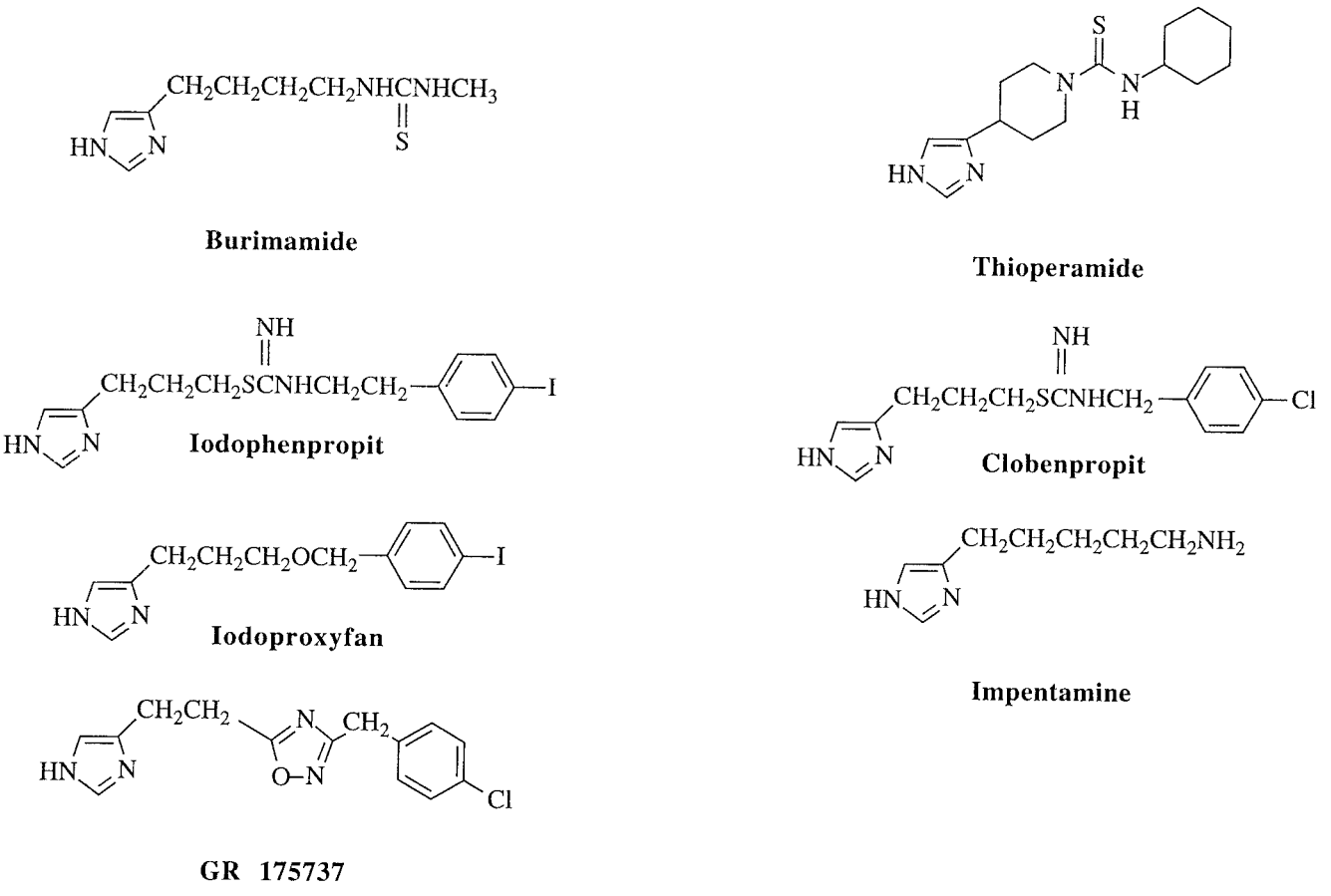

FIG. 7. Histamine H_3-receptor antagonists.

imately 70 kDa (Cherifi et al., 1992). However, it remains to be established whether this protein is the histamine H_3-receptor.

D. Signal Transduction Mechanisms

The signal transduction pathways used by the histamine H_3-receptor remain largely subject to speculation, but there is increasing evidence to suggest that this receptor belongs to the superfamily of G-protein–coupled receptors. Evidence for this has largely been obtained from ligand-binding studies involving the modulation by guanine nucleotides of H_3-agonist binding (Arrang et al., 1990; West et al., 1990; Kilpatrick and Michel, 1991; Zweig et al., 1992; Clark and Hill, 1995) and of H_3-agonist inhibition of ^{3}H-antagonist binding (Jansen et al., 1992, 1994; Ligneau et al., 1994). The most direct evidence for a functional H_3-receptor–G-protein linkage has come from studies of [^{35}S]GTPγS binding to rat cerebral cortical membranes (Clark and Hill, 1996). In the presence of H_1- and H_2-receptor antagonists (0.1 μM mepyramine and 10 μM tiotidine), both R-α-methylhistamine and N^{α}-methylhistamine produced a concentration-dependent stimulation of [^{35}S]GTPγS binding (EC_{50} = 0.4 and 0.2 nM, respectively) in rat cerebral cortical membranes (Clark and Hill, 1996). Furthermore, this response was abolished by pretreatment of membranes with pertussis toxin, implying a direct coupling to a G_i or G_o protein (Clark and Hill, 1996). Evidence for an involvement of pertussis toxin-sensitive G-proteins in the response to H_3-receptor stimulation has also come from studies of histamine H_3-receptor signaling in human and guinea pig heart (Endou et al., 1994; Imamura et al., 1995). In these tissues, histamine H_3-receptor–stimulation seems to lead to an inhibition of N-type Ca^{2+} channels responsible for voltage-dependent release of noradrenaline (Endou et al., 1994; Imamura et al., 1995).

Very little is known about the intracellular signal transduction pathways initiated by histamine H_3-receptor activation. Several research groups have failed to observe an inhibition of adenylyl cyclase activity in different tissues and cells (Garbarg et al., 1989; Schlicker et al., 1991; Cherifi et al., 1992), which might indicate that H_3-receptors preferentially couple to G_o proteins. There is one interesting report of a negative coupling to phospholipase C in the HGT-1 gastric tumor cell line (Cherifi et al., 1992), but this observation needs confirmation by other research.

V. Other Responses to Histamine

A. Potentiation of Responses to N-Methyl-D-Aspartate

Studies in hippocampal cell cultures, acutely dissociated neurons, and *Xenopus* oocytes expressing the re-

combinant N-methyl-D-aspartate (NMDA) receptor subunits NR2B and NR1 have shown that histamine is able to enhance NMDA-activated currents, independently of the known histamine receptors, via a mechanism that probably involves the polyamine-binding site on the NMDA-receptor complex (Bekkers, 1993; Vorobjev et al., 1993; Williams, 1994; Saysbasili et al., 1995). Histamine and the polyamines spermine and spermidine have also been shown to enhance glutamate toxicity in human NT2-N neurons (Munir et al., 1996). Interestingly, attempts to demonstrate a similar effect of histamine on NMDA-induced currents in rat hippocampal slices, or outside-out patches pulled from the somas of these cells, were without success (Bekkers et al., 1996). However, two studies using conventional and whole cell recording of neurons in the CA1 region of slices of rat hippocampus concluded that the modulation of NMDA-mediated synaptic currents was dependent upon pH (Saysbasili et al., 1995; Janovsky et al., 1995). Thus, at low pH (7.2), histamine enhanced synaptic currents, whereas at pH 7.6 it reduced them. Interestingly, at physiological pH (7.4), no significant action of histamine was seen (Saysbasili et al., 1995).

B. A Role as an Intracellular Messenger?

Although most actions of histamine can be attributed to an extracellular action, there are reports that histamine may have intracellular actions. The activity of the enzyme, histidine decarboxylase, which catalyzes the formation of histamine from histidine, has been observed to be high in several tissues undergoing rapid growth or repair (Ishikawa et al., 1970; Kahlson and Rosengren, 1971; Watanabe et al., 1981; Bartholeyns and Bouclier, 1984; Bartholeyns and Fozard, 1985). These observations have led to the proposal that newly synthesized (nascent) histamine may have a role in cellular proliferation, perhaps via an intracellular site. Some evidence has been accumulated that intracellular histamine levels (or the activity of histidine decarboxylase) can be regulated by tumor-promoting phorbol esters (Saxena et al., 1989). Furthermore, Brandes and colleagues (Saxena et al., 1989; Brandes et al., 1990, 1992) have suggested that N, N-diethyl-2-[4-(phenylmethyl)-phenoxy]ethanamine (DPPE) might be an inhibitor of a specific intracellular histamine receptor (H_{IC}). However, at the present time, the evidence in favor of an intracellular histamine receptor has not been generally accepted, and alternative possibilities need to be explored. For example, the direct effects of histamine, or its analogues, on polyamine sites (Vorobjev et al., 1993; Bekkers, 1993) and heterotrimeric G-proteins (Hagelüken et al., 1995; Seifert et al., 1994) could explain many of the observations to date.

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