CHAPTER

16

Histamine

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OUTLINE

INTRODUCTION

Histamine is a signaling molecule in the stomach, the skin, the immune and nervous systems. The posterior hypothalamus is the sole source of histamine-containing neurons, which innervate the whole central nervous system and are active exclusively during waking. Three of the four known metabotropic histamine receptors are widely expressed in the brain. H_1 and H_2 are mostly excitatory; H_3 is an inhibitory auto- and heteroreceptor. Mutual interactions with other aminergic and peptidergic systems form a network that links basic homeostatic and higher brain functions including sleep–waking regulation, energy administration, feeding, drinking, synaptic plasticity, learning and memory.

HISTAMINE: THE MOLECULE AND THE MESSENGER

Histamine is a mediator of several physiological and pathological processes within and outside of the nervous system

Although the existence of histamine in the brain was known over 50 years ago, a role for this substance in brain function was not widely appreciated until relatively recently. It is now clear that histamine is formed within and released from central nervous system neurons, and is an important regulator of several brain functions (Haas & Panula, 2003; Haas et al., 2008). Paradoxically, the existence of well-established roles for histamine outside of the nervous system is one factor that hampered the acceptance of this amine as a neuronal messenger. As a physiological mediator, histamine is best known as an endogenous stimulant of gastric secretion. Histamine is also released from mast cells and basophils by antigens, certain peptides, and small basic drugs. In addition, histamine participates in inflammation and in the regulation of immune responses. Cardiac stores of histamine probably play no physiological role, but may be of pathological significance. Endogenous peripheral histamine may also participate in the modulation of sympathetic and afferent nerve activity.

The chemical structure of histamine has similarities to the structures of other biogenic amines, but important differences also exist

Chemically, histamine is 2-(4-imidazolyl)ethylamine. The ethylamine "backbone" is a common feature of many of the amine transmitters (e.g., dopamine, norepinephrine and serotonin). However, the imidazole nucleus, absent from other known transmitters, endows histamine with several distinct chemical properties. Among these is prototypic tautomerism, a property that permits it to exist in two different tautomeric forms. The tautomeric properties of histamine are thought to be critical to the ability of this molecule to activate some of its receptors. Although histamine has more than one basic center, both tautomers exist predominantly as monocations at physiological pH (Fig. 16-1).

HISTAMINERGIC CELLS OF THE CENTRAL NERVOUS SYSTEM: ANATOMY AND MORPHOLOGY

The brain stores and releases histamine from more than one type of cell

Mast cells are a family of bone marrow–derived secretory cells that store and release high concentrations of histamine. They are found throughout many connective tissues of the body, but are also present within and surrounding the brain of many species (Schwartz et al., 1991). In many species, they are prevalent in thalamus and hypothalamus, as well as in the dura mater, leptomeninges and choroid plexus. The quantitative contribution made by mast cells to brain histamine levels can be substantial in some cases (e.g., rat thalamus). Earlier biochemical studies suggested that histamine in brain mast cells could be distinguished from neuronal histamine by characteristics such as histamine turnover rates, subcellular fractionation and ontogenic pattern (Schwartz et al., 1991). However, activated mast cells may, like neurons, show a fast histamine turnover rate. Brain and dural mast cells have been characterized histologically and histochemically in detail. Characterization of neuronal and non-neuronal histamine has been facilitated by the study of mast cell–deficient mice and rats.

Several functions for brain and dural mast cells are investigated

The close proximity of these cells to blood vessels, along with the potent vascular actions of their contents, has led to the suggestion that they respond to and regulate blood flow, permeability and immunological access to the brain. Dural mast cells are also found near sensory nerve fibers, where they can modulate the release of inflammatory neural mediators, promoting inflammation and pain (Hough & Rice, 2011). Brain/dural mast cells are also thought to participate in chronic neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease and Wernicke's encephalopathy (Langlais et al., 2002). Mast cell–astrocyte signaling may be important in some of these conditions (Kim et al., 2010). Mast cells respond to chemosensory cues associated with estrus induction (Kriegsfeld et al., 2003). In addition to mast cells and neurons, other brain cells (e.g., cerebrovascular endothelial cells) (Schwartz et al., 1991) may also synthesize and/or store histamine.

Histaminergic fibers originate from the tuberomamillary (TM) region of the posterior hypothalamus

In the past, researchers' inability to visualize histaminergic neurons greatly limited the understanding and acceptance of this neuronal system. This changed in 1984, when antibodies raised against histamine (Panula et al., 1984) or its biosynthetic enzyme histidine decarboxylase (HDC, EC 4.1.1.22) (Watanabe et al., 1984) provided the first detailed anatomical studies of these cells and their distribution. In all vertebrates studied, including humans, histaminergic neurons are found in the TM nucleus of the posterior basal hypothalamus (Fig. 16-2).

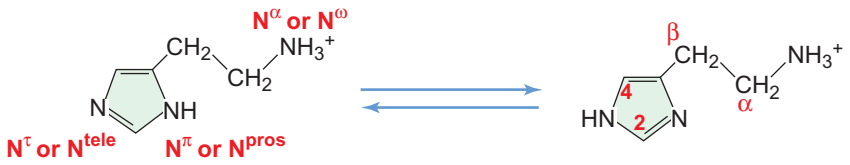

FIGURE 16-1 **Chemical structure of histamine, illustrating the two tautomeric forms.** The names of the nitrogen atoms are shown on the left tautomer and the numbering scheme for carbon atoms is on the right. For example, N^t-methylhistamine, Nα-methylhistamine and α-methylhistamine are distinct substances and have very different properties (Fig. 16-3 and Table 16-1). This nomenclature system avoids reference to the ring nitrogens as 1- and 3-, a designation that becomes confused by the tautomerism.

Histaminergic neurons have morphological and membrane properties that are similar to those of neurons storing other biogenic amines

Histaminergic perikarya can be of medium size, but most are large bipolar or multipolar cells, with diameters of up to 30 μm. Their ultrastructural characteristics resemble those of other aminergic cell bodies (Haas & Panula, 2003; Haas et al., 2008). Some of the ventrally located cells may make direct contact with cerebrospinal fluid. Histamine neurons can take up L-DOPA and produce and release dopamine.

Histaminergic neurons display a behavioral state–dependent spontaneous activity of about 2 Hz. A combination of sodium, calcium and potassium conductances accounts for their pacemaker properties (Haas et al., 2008), which resemble those of catecholaminergic and serotonergic neurons. TM histaminergic neuron firing is high during waking or attention and absent during sleep; the histaminergic neurons represent a major waking system (Anaclet et al., 2009; Lin et al., 2011a).

Histaminergic fibers project widely to most regions of the central nervous system

Both ascending and descending efferent pathways account for the histaminergic innervation of the mammalian brain and spinal cord (Fig. 16-2). The ascending tracts are predominantly ipsilateral. Although all cell groups are thought to contribute to all pathways, new studies of histamine release suggest that not all TMN neurons are identical, but rather are likely to be organized into functionally distinct circuits (Giannoni et al., 2009). Although nearly all CNS areas contain some histaminergic fibers, the density of innervation is heterogeneous (Haas & Panula, 2003; Inagaki et al., 1988; Panula et al., 1989) and somewhat phylogenetically distinct. The highest densities are found in several hypothalamic nuclei, the medial septum, the nucleus of the diagonal band and the ventral tegmental area and moderate densities in cerebral cortex, amygdala, striatum and substantia nigra. Innervation of the hippocampus and thalamus is substantial in some species. Most areas of the brainstem, as well as retina, cerebellum and spinal cord contain only small numbers of fibers. These densities follow closely the tissue concentrations of histamine and its biosynthetic enzyme found throughout the brain (Hough & Green, 1984). In the monkey brain, a homogeneous innervation of several areas of the visual system (including lateral geniculate and superior colliculus) has been documented. Ultrastructural studies in rat show that histaminergic varicosities form only a few synaptic contacts, implying that most neuronal histamine is released by nonsynaptic mechanisms; this is the case for the other amine transmitter systems as well (Haas et al., 2008). Histaminergic varicosities also appear to make contact with glia and blood vessels.

A number of substances and important enzymes are co-localized with histamine and its biosynthetic enzyme in hypothalamic tuberomamillary neurons (Onodera et al., 1994). These include glutamate decarboxylase, GABA, GABA-transaminase, adenosine deaminase and monoamine oxidase-B. The neuropeptides methenkephalin and galanin and thyrotropin-releasing hormone (TRH) are present in some histaminergic neurons. These peptides, as well as GABA, may function as co-transmitters here. Galanin can reduce histamine release by inhibiting TM neuron firing and at axonal locations, similar to its proposed actions on cholinergic and serotonergic fibers (Fig. 16-7). Endogenous GABA from preoptic and hypothalamic afferents inhibits TM neuron firing and thus regulates neuronal histamine release (Haas et al., 2008). GABA storage within TM neurons is separate from that of histamine (Kukko-Lukjanov et al., 2003).

TM histaminergic cells receive innervation from several brain regions, including the infralimbic prefrontal cortex, the septum/diagonal band complex, the preoptic area and the hypothalamus. These or other afferents contain neuropeptide Y (NPY), thyrotropin releasing hormone (TRH), orexins or substance P (Haas et al., 2008). TM cells receive input from adrenergic (C1–C3), noradrenergic (A1–A2) and serotonergic (B5–B9) cells, but the innervation from the dopamine-containing ventral tegmental area is sparse (Haas & Panula, 2003). Histamine neurons are excited through activation of dopamine D2 receptors. Since some of these areas have both input and output connections with histaminergic neurons, reciprocal control has been considered.

Histaminergic neurons are present in many species. Histaminergic neurons have been found in the hypothalamus or diencephalon of a variety of vertebrate brains, including those of fish, snake, turtle and bird. The brain histaminergic system of zebrafish has been studied in detail, since this species apparently lacks any non-neuronal stores of histamine, such as those found in gastric mucosa or mast cells in mammals (Haas et al., 2008). In invertebrates, histamine functions as an important transmitter, for example, in arthropod and insect photoreceptors *hcl*A, *hcl*B (Pantazis et al., 2008) and in mollusks; the C2 neuron of *Aplysia* uses histamine as a transmitter.

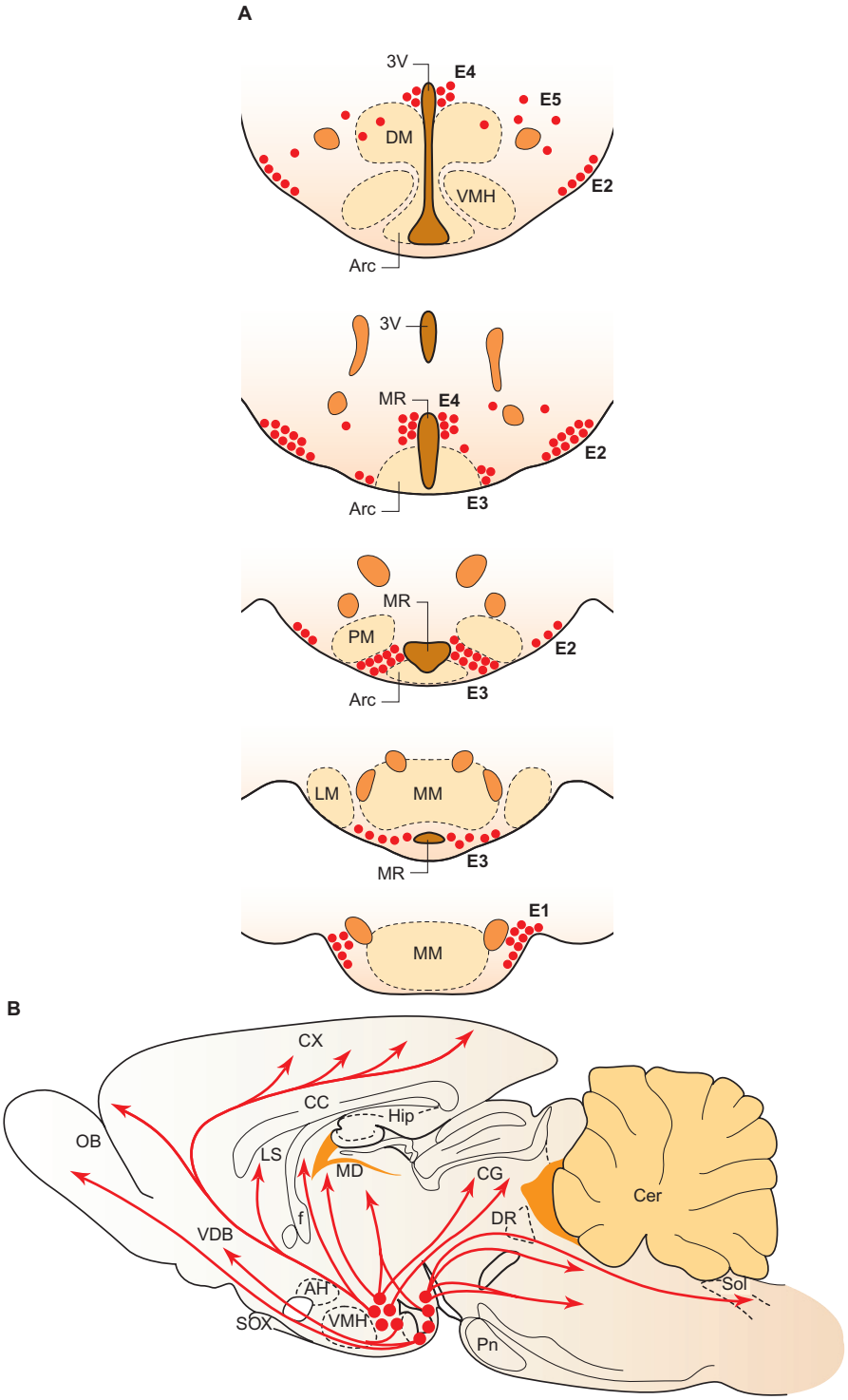

FIGURE 16-2 **The histaminergic system of the rat brain. (A)** Frontal sections through the posterior hypothalamus showing the location of histaminergic neurons. Arc, arcuate nucleus; DM, dorsomedial nucleus; LM, lateral mammillary nucleus; MM, medial mammillary nucleus; MR, mammillary recess; PM, premammillary nucleus; 3V, third ventricle; VMH, ventromedial hypothalamic nucleus. (Modified with permission from Schwartz et al., 1991). **(B)** A sagittal view illustrating the major ascending and descending fiber projections. AH, anterior hypothalamus; CC, corpus callosum; Cer, cerebellum; CG, central gray; CX, cerebral cortex; DR, dorsal raphe; f, fornix; Hip, hippocampus; LS, lateral septum; MD, mediodorsal thalamus; OB, olfactory bulb; Pn, pontine nuclei; Sol, nucleus of solitary tract; SOX, supraoptic decussation; VDB, vertical limb of the diagonal band; VMH, ventromedial hypothalamic nucleus. (Adapted from Hough & Leurs, 2002)

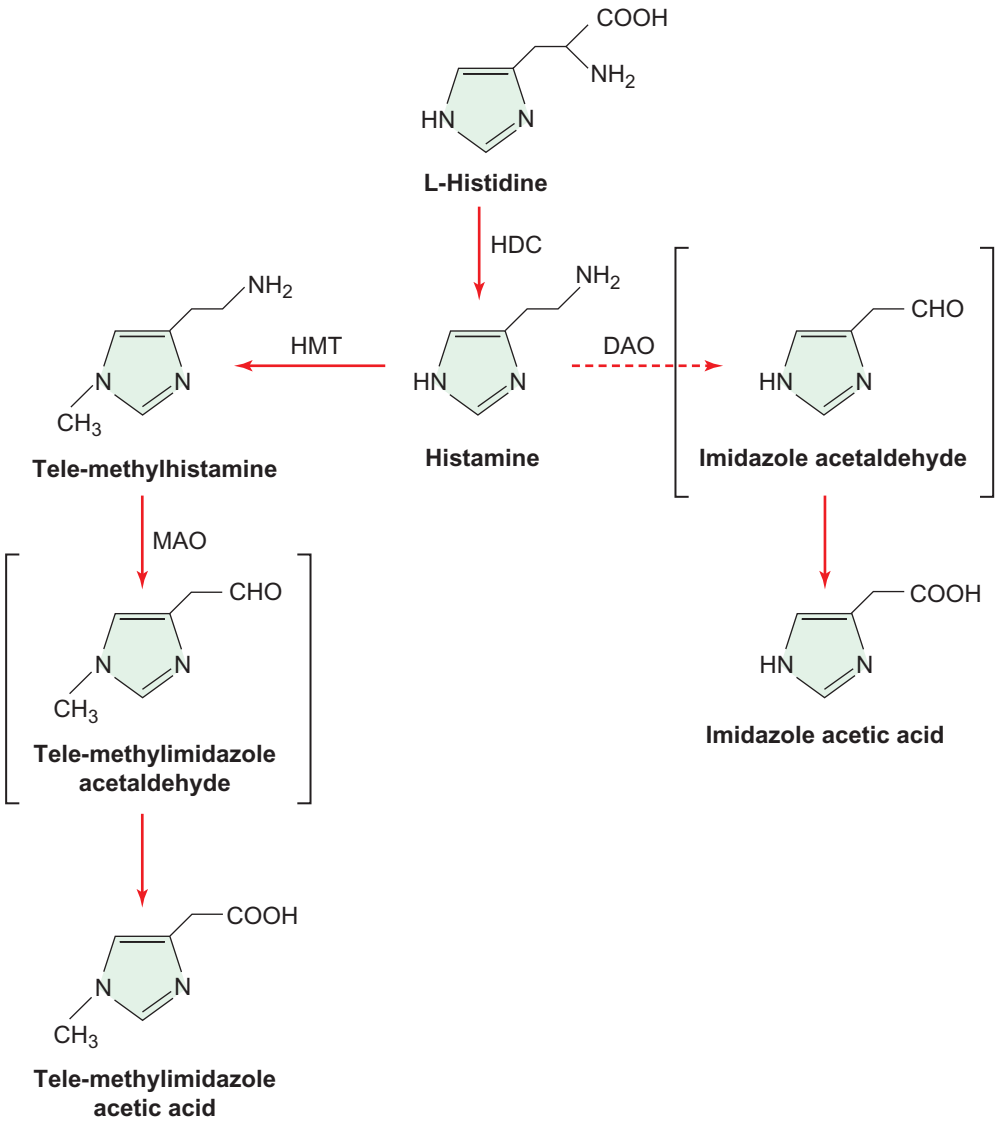

FIGURE 16-3 **Synthesis and metabolism of histamine.** Solid lines indicate the pathways for histamine formation and catabolism in brain. Dashed lines show additional pathways that can occur outside the nervous system. HDC, histidine decarboxylase; HMT, histamine methyltransferase; DAO, diamine oxidase; MAO, monoamine oxidase. Aldehyde intermediates, shown in brackets, have been hypothesized but not isolated.

DYNAMICS OF HISTAMINE IN THE BRAIN

Specific enzymes control histamine synthesis and breakdown

Figure 16-3 summarizes the major mechanisms for the synthesis and metabolism of histamine. Biosynthesis is performed in one step by the enzyme L-histidine decarboxylase (HDC, E.C. 4.1.1.22). Histamine metabolism occurs mainly by two pathways. Oxidation is carried out by diamine oxidase (DAO, E.C. 1.4.3.6), leading to imidazole acetic acid (IAA), whereas methylation is effected by histamine N-methyltransferase (HMT, E.C. 2.1.1.8), producing tele-methylhistamine (t-MH). IAA can exist as a riboside or ribotide conjugate. t-MH is further metabolized by MAO-B, producing tele-methylimidazole acetic acid (t-MIAA). Note that histamine is a substrate for DAO but not for MAO. Aldehyde intermediates, formed by the oxidation of both histamine and t-MH, are thought to be quickly oxidized to acids under normal circumstances. In the vertebrate CNS, histamine is almost exclusively methylated and only small amounts of DAO are detectable. However, IAA, a GABA agonist, has been detected and can be formed in the rat brain in small amounts. Although IAA in the brain is probably normally formed by the transamination of histidine, it can also be formed by histamine oxidation under some circumstances. The IAA ribotide has been suggested to be an endogenous ligand for brain imidazoline receptors. In some invertebrate nervous systems, histamine is metabolized by conjugation with amino acids to dipeptides (e.g., γ-glutamylhistamine).

Several forms of histidine decarboxylase (HDC) may derive from a single gene

A single cDNA, cloned from rat, mouse and human cells, encodes a 74-kDa protein with functional HDC activity. Two species of HDC mRNA have been found in some cells, but the larger one, which contains an additional insert sequence, does not encode a functional enzyme and is not found in brain. Consistent with the immunohistochemical studies discussed above, HDC mRNA is localized to the caudal hypothalamus in rats. The human HDC gene is large, composed of 12 exons with a size of about 2.4 kb. The enzyme, which requires pyridoxal-5′-phosphate as a coenzyme, shares some homology with DOPA decarboxylase (Chap. 14), another enzyme that requires this cofactor. Protein purification studies have shown HDC to be a dimer composed of two identical 55-kDa subunits. Post-translational modification of the enzyme occurs by an elastase-like enzyme, which converts the 74-kDa form to the smaller protein. Biochemical, biophysical and immunological studies show clear evidence for the existence of HDC isoenzymes (Fleming & Wang, 2003). Either post-translational modification of the protein or, possibly, allelic variants may contribute to the existence of these isoforms. The rat HDC gene encodes for two potential N-glycosylation sites and two recognition sequences for phosphorylation. HDC phosphorylation by either cAMP-dependent protein kinase A (PKA) or calcium calmodulin-dependent protein kinase II (CamKII) increases brain histamine synthesis. Dephosphorylation by either protein phosphatase2A (PP2A) or protein phosphatase 1 (PP1) decreases brain histamine synthesis through an HDC mechanism (Moreno-Delgado et al., 2007).

Histamine synthesis in the brain is controlled by the availability of l-histidine and the activity of HDC

Although histamine is present in plasma, it does not penetrate the blood–brain barrier, and thus histamine concentrations in the brain must be maintained by synthesis. With a Km value of 0.1 mM for L-histidine under physiological conditions, HDC is not saturated by histidine concentrations in the brain, an observation that explains the effectiveness of large systemic doses of this amino acid in raising the concentrations of histamine in the brain. The essential amino acid L-histidine is transported into the brain by a saturable, energy-dependent mechanism (Schwartz et al., 1991). Subcellular fractionation studies show HDC to be localized in cytoplasmic fractions of isolated nerve terminals, that is, synaptosomes.

HDC activity can be regulated by both hormonal and neuronal factors, most of which are poorly understood. Phosphorylation of the enzyme by PKA may be an important regulatory mechanism. Several regulatory sites have recently been found in the promoter region of the gene. Unlike catecholamines and indoleamines, histamine itself is not a direct inhibitor of its biosynthetic enzyme, but it exerts feedback control through the H_3 autoreceptor. A highly selective and potent "suicide" inhibitor of HDC, S-α-fluoromethylhistidine, has been used very successfully to study the functions of histamine in brain.

Histamine is stored within and released from neurons

Histamine is stored within and released from neurons, but a neuronal transporter for histamine has not been found. Newly synthesized neuronal histamine is transported into TM neuronal vesicles by the vesicular monoamine transporter VMAT2 (Kukko-Lukjanov et al., 2003). Both in vivo and in vitro studies show that depolarization of nerve terminals activates the exocytotic release of histamine by a voltage- and calcium-dependent mechanism. Once released, histamine activates both postsynaptic and presynaptic receptors. Unlike the nerve terminals from other amine transmitters, however, histaminergic nerve terminals do not exhibit a high-affinity uptake system for histamine (Schwartz et al., 1991; Kukko-Lukjanov et al., 2003). Astrocytes may contain a histamine transport system.

In the vertebrate brain, histamine metabolism occurs predominantly by methylation

HMT, the histamine-methylating enzyme, uses the methyl donor S-adenosyl-L-methionine. The enzyme has a Km of about 10 μM for both histamine and the methyl cofactor, and has been localized to the soluble subcellular fraction. Antibodies raised against a highly purified kidney enzyme with a molecular weight of 33,000 co-precipitate the brain enzyme, showing strong similarities between the proteins. A 1.3-kb cDNA has been cloned and expressed in Escherichia coli; the encoded protein shows the characteristics of the natural enzyme (Takemura et al., 1992). Early studies suggested that isoforms of HMT might exist, but no enzymatically active splice variants have been identified. The HMT gene can be spliced to produce a shorter form (HMT-S; Barnes et al., 2004). Although HMT-S mRNA is present in human brain and placenta, the protein does not methylate histamine and its biological significance remains unclear. HMT is subject to inhibition by both its product, t-MH, and, at higher concentrations, its substrate histamine. Experimental inhibitors of HMT include metoprine and SKF91488. These agents have been used in metabolic studies, as well as to probe functions for CNS histamine. As expected, they increase histamine concentrations in the brain and reduce the concentrations of t-MH and t-MIAA. Many other compounds can also inhibit HMT. For example, tacrine, a cholinesterase inhibitor used to treat Alzheimer's disease, also inhibits HMT at therapeutic doses.

Neuronal histamine can be methylated outside of histaminergic nerve terminals

In contrast to the striking regional distribution of histamine and HDC, HMT shows a more even distribution, suggesting a widespread HMT localization. In support of this, lesions that destroy histaminergic fibers cause large reductions in HDC concentrations but with a lesser effect on brain HMT activity. The existence of glial cell lines containing HMT seemed to support an extraneuronal localization for histamine metabolism. Because HMT does not follow the characteristic regional distribution of histamine and HDC, yet the

HMT product t-MH does show this distribution, it is thought that the formation of t-MH is limited by the rate of histamine release from neurons. The rate at which histamine is formed and methylated (i.e, the histamine turnover rate) also follows this characteristic regional pattern, and thus reflects the activity of histaminergic neurons. The hypothesis that histamine is methylated following its neuronal release is supported by recent work showing that extracellular histamine is methylated by isolated nerve terminal fractions to a much greater extent than it is transported (Barnes et al., 2004). The same study showed the existence of a membrane-bound form of HMT that could methylate newly released histamine in a manner analogous with that of acetylcholinesterase in the cholinergic system. However, attempts to clone a unique membrane-bound form of this enzyme have not succeeded (Barnes et al., 2004).

The product of histamine methylation, t-MH, is a substrate for MAO-B and is ultimately oxidized to t-MIAA, the end product of brain histamine metabolism. Thus, MAO inhibitors increase brain t-MH concentrations and lower t-MIAA concentrations, with little or no effect on histamine concentrations. Both t-MH and t-MIAA have been detected in brain and CSF. In the brain, t-MIAA concentrations are unaffected by probenecid, an inhibitor of the brain transport of other transmitter metabolites.

A polymorphism in human HMT (Thr105Ile) may be an important regulatory factor in some human disorders

The Thr105Ile polymorphism, associated with decreased enzyme activity and presumed increases in tissue HA levels, has an increased prevalence in allergic rhinitis, some forms of urticaria, Parkinson's disease, essential tremor, attention deficit hyperactivity disorder and alcoholism. Increased histamine levels in patients with atopic dermatitis may result, at least in part, from reduced inactivation via HMT. Similar studies of multiple sclerosis, migraine, schizophrenia and Alzheimer's patients found no such increased prevalence (Kennedy et al., 2008).

The activity of histaminergic neurons is regulated by H_3 autoreceptors and by other transmitter receptors

The observation that histamine can inhibit its own synthesis and release from brain slices and synaptosomes led to the discovery of the histamine H_3 autoreceptor, a hypothesis which was confirmed by the development of unique agonists and antagonists of this receptor (Table 16-1; Arrang et al., 1987; Arrang et al., 1995). The H_3 antagonist thioperamide enhances the firing rate of histaminergic neurons and increases neuronal histamine release, brain histamine turnover rates and t-MH concentrations in the brain. H_3 agonists, such as R-α-methylhistamine and immepip, produce the opposite effects. H_3 agonists and antagonists are important tools for understanding the brain histamine system, and several new agents are currently being developed for clinical uses.

The stimulatory effects of H_3 antagonists on brain histamine dynamics were initially attributed to the competitive antagonism of continuously released neuronal histamine, which stimulates the H_3 autoreceptors. However, since there are known to be H_3 antagonists that do not increase brain histamine release, it is now thought that the inverse agonist activity of certain H_3 ligands accounts for their activation of the histaminergic system (Morisset et al., 2000). This explanation, consistent with in vitro studies on recombinant H_3 receptors (see below), would mean that ongoing in vivo H_3 autoreceptor activity is constitutive, and therefore does not depend on histamine-induced H_3 activation. This conclusion does not mean that spontaneous, neuronal histamine release is not occurring; only that it may not be continuously reaching and stimulating its autoreceptors.

MOLECULAR SITES OF HISTAMINE ACTION

Histamine acts on four G-protein–coupled receptors (GPCRs), three of which are clearly important in the brain

Table 16-1 summarizes the characteristics of known histamine receptors in mammals. These histamine receptors subtypes are all linked to G proteins, and all of them have been found inside and outside the brain. Within the brain, the H_1, H_2 and H_3 receptors all have unique regional distributions but none is localized exclusively to neurons. For the recently discovered H_4 receptor, only limited information on its brain localization is currently available. Selective agonists and antagonists are also available for each of the histamine receptors (Leurs et al., 1995). The judicious use of these compounds for receptor classification and discovery has been reviewed extensively (Hill et al., 1997; Hough, 2001).

H_1 receptors are intronless GPCRs linked to G_q and calcium mobilization

The H_1 receptor protein was successfully cloned from a cDNA library of bovine adrenal medulla (Yamashita et al., 1991). This protein is encoded by a single exon and contains 486 (rat), 488 (guinea pig, mouse), 491 (bovine) or 487 (human) amino acids. The homology between the several receptor proteins is quite high in some intracellular domains (90%), but is significantly lower in other intracellular and extracellular regions. Features common to many of the G-protein–coupled receptors are present, including seven transmembrane domains, N-terminal glycosylation sites and phosphorylation sites for protein kinase A (PKA) and protein kinase C (PKC). The third cytoplasmic loop is large, characteristic of other phosphoinositide-specific phospholipase C (PLC)-linked receptors (see below). Interestingly, natural alleles of the H_1 receptor control both the autoimmune T cell and vascular responses regulated by histamine after pertussis toxin sensitization; the H_1 receptor is identical with Bphs, an autoimmune disease locus (Ma et al., 2002).

TABLE 16-1 Characteristics of Histamine Receptors in the Brain

Characteristics	H_1	H_2	H_3	H_4
Cloned?	Yes	Yes	Yes	Yes
Gene localization (mouse)	Chromosome 6	Chromosome 13	Chromosome 2	Chromosome 18
Effectors	PLC: $+IP_3$ [$+Ca^{2+}$, +cGMP, +NO]	+cAMP + PLC: Ca^{2+}, IP_3[§]	−cAMP	−cAMP
	PLC: +DAG [+PKC]		−NHE	+MAP kinase
	PLA_2: +AA, $+TXA_2$		$-Ca^{2+}$	$+Ca^{2+}$
			+MAP kinase	
Conductances[‖]	Excit: ↑ Cation	Excit: ↑ I_H	Reduced cell firing, inhibition of Ca^{2+} channels	Hyperpolarisation, outward current
Currents	Excit: ↓ K_{Leak}	Inhib: ↑ K_{V3}		
	Inhib: ↑ K_S	Excit: ↓ I_{kCa}		
Selective agonists	2-thiazolylethylamine, histaprodifen	Amthamine	R-α-methylhistamine*[¶]	4-methyl-histamine
			Immepip*[¶]	VUF8430
			Immethridine	
Antagonists	Pyrilamine (mepyramine)*	Ranitidine	Thioperamide*[¶]	Thioperamide*[¶]
		Zolantidine*	Clobenpropit*[¶]	Iodophenpropit*[¶]
			Ciproxyfan*	J&J7777120
Radioligands	^{3}H-pyrilamine	^{125}I-iodoaminopotentidine	^{3}H-N$^{\alpha}$-methylhistamine	[^{3}H]-histamine
	^{125}I-iodobolpyramine		^{125}I-iodophenpropit	[^{3}H]-J&J7777120
			^{125}I-iodoproxyfan	
Distribution[†‡]	Hypothalamus, aminergic nuclei brain stem, cerebellum, thalamus, cortex, hippocampus	Cerebral cortex, striatum, nucleus accumbens, hippocampus, amygdala, cortex	Striatum, nucleus accumbens, cerebral cortex, substantia nigra, ventral and dorsal striatum	Hippocampus, cortex, striatum, thalamus, amygdala

The characteristics of the four major classes of histamine receptors are summarized. Question marks indicate suggestions from the literature that have not been confirmed. AA, arachidonic acid; DAG, diacylglycerol; $I_{kCa}{}^{2+}$, calcium-activated potassium current; IP_3, inositol 1,4,5-trisphosphate; NHE, sodium–proton exchange, PKC, protein kinase C; NO, nitric oxide; PLC, phosphoinositide-specific phospholipase C; TXA_2, thromboxane A_2.
*Has brain-penetrating characteristics after systemic administration.
[†]All receptors may exist in non-neuronal brain tissue as well.
[‡]Distribution in guinea pig (H_1 and H_2) and rodent (H_3, H_4) brain. For the H_1 receptor, distribution is very different across species.
[§]Contradictory findings have been reported.
[¶]Compounds show activities at both H_3 and H_4 receptors.
[‖]see Haas and Panula (2003) for details, including abbreviations for conductance changes.

H_1-linked intracellular messengers

Activated H_1 receptors are known to activate a pertussis toxin–insensitive G protein, G_q, that stimulates PLC, with the subsequent generation of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) (see Chap. 23). These two mediators are known to elevate intracellular Ca^2 concentrations and to activate PKC, respectively (Leurs et al., 1994). Both internal and external Ca^{2+} sources are required to initiate and maintain responses. The distribution of H_1-activated IP_3 concentrations in the brain corresponds well to the distribution of H_1 receptor binding sites in the guinea pig (Schwartz et al., 1991).

H_1 receptors also can activate phospholipase A_2 (PLA_2), with the subsequent release of arachidonic acid and its metabolites. In platelets, this response does not require activation of the phosphoinositide cycle and is inhibited by pertussis toxin, suggesting a second, distinct $G_{i/o}$-protein–mediated transduction mechanism. In cells transfected with the H_1 receptor, PLA_2 activation is partially inhibited by pertussis toxin, also suggesting at least two transduction systems (Leurs et al., 1994; Leurs et al., 1995).

H_1 receptor activation stimulates glycogen metabolism (Schwartz et al., 1991) and positively modulates receptor-linked cAMP synthesis. The activation of brain cAMP synthesis by histamine is a well-studied phenomenon that reveals a positive interaction between histamine receptors (Hill, 1990). H_1 receptors do not directly stimulate adenylyl cyclase but rather enhance the H_2 stimulation, probably through the

effects of calcium and PKC activation on sensitive adenylyl cyclase isoforms (see Chap. 22). Activation of brain H_1 receptors also stimulates cGMP synthesis (Prell & Green, 1986). Outside the brain, histamine is known to relax vascular smooth muscle by activation of endothelial H_1 receptors, thereby increasing endothelial Ca^{2+} concentrations and stimulating the synthesis and release of nitric oxide. The latter, a diffusible agent, then activates the smooth muscle guanylyl cyclase (Leurs et al., 1995). Although less is known about these mechanisms in the CNS, there is evidence that brain H_1 receptor activation can produce effects that depend on guanylyl cyclase activity (Prell & Green, 1986).

H_1 receptor activation induces depolarizing responses in many brain areas, notably hypothalamus, thalamus and cerebral cortex. In vertebrate brain, many of these effects are mediated by opening cation channels. H_1-induced excitation can also occur by blockade of K_{Leak} conductances (Haas & Panula, 2003). In other cases, however, H_1 receptors can cause inhibition by activating certain Ca^{2+}-dependent potassium channels. Most of the H_1 receptor-induced conductance changes are mediated by the $IP_3 - Ca^{2+}$ cascade.

H_2 receptors are intronless GPCRs linked to G_s and cyclic AMP synthesis

The H_2 receptor cDNA has been cloned from several species, including dog, rat, guinea pig, mouse and man (Leurs et al., 1995; Arrang et al., 1995). Use of the polymerase chain reaction (PCR) with degenerate oligonucleotides and canine gastric parietal cDNA led to the cloning of the first H_2-receptor gene (Gantz et al., 1991). These intronless genes encode for receptor proteins having 358–359 amino acids with a molecular weight of approximately 40,000 and show the typical features of GPCRs. Like the H_1 receptor, the H_2 protein has sites for phosphorylation by PKC and for glycosylation. Unlike the former, the latter lacks a consensus site for PKA. The H_2 receptor shows only about a 40% homology with the H_1 receptor and shows some features that are often observed for receptors known to be positively coupled to adenylyl cyclase. Features include a short third cytoplasmic loop and a long C-terminal cytoplasmic tail (Leurs et al., 1995; Arrang et al., 1995). The human H_2 receptor gene is located on chromosome 5. When expressed in cells, the cloned H_2 receptor shows binding profiles and biochemical characteristics that closely resemble the natural receptor. Both neuronal and non-neuronal cells of brain possess H_2 receptors (Haas & Panula, 2003; Schwartz et al., 1991). H_2 receptors are abundant in the cerebral cortex, corpus striatum and nucleus accumbens of the guinea pig brain (Table 16-1). In the rat, characterization of brain H_2 receptors has been hampered by low concentrations of receptor; however, H_2 receptor mRNA has been observed in this species.

H_2-linked intracellular messengers

H_2 receptors are linked to increases in cAMP but also to other intracellular signals. It is well established that H_2 receptors lead to increases in cAMP concentrations in many tissues by stimulation of adenylyl cyclase (Hill, 1990). Cells transfected with H_2 receptors demonstrate activation of adenylyl cyclase, confirming that cAMP is an important H_2 messenger. Since this effect is blocked by cholera toxin, a G_s-type protein is implicated in mediating these effects. Elevated cAMP concentrations then result in the activation of protein kinase A (PKA), leading to numerous cellular changes (see Ch. 22). The second messenger cAMP is thought to be responsible for most of the effects of H_2 receptor stimulation. However, H_2 receptors activate adenylyl cyclase in homogenates from several regions of guinea pig brain, but the density of H_2-binding sites does not correlate with the magnitude of cyclase activation across regions. These and other experiments suggest that this receptor also uses additional transduction mechanisms, including activation of PLC, increased intracellular Ca^{2+}, increased IP_3 concentrations, increased phospholipid methylation and decreased arachidonate release (Hill, 1990; Leurs et al., 1995; Arrang et al., 1995). Both G_s and G_q proteins have been implicated in these responses, suggesting that the H_2 receptor can activate more than one type of G protein. Similar conclusions have been reached in studies of other GPCRs. Further studies are needed to address the importance of the various signal transduction pathways for H_2 receptor function.

H_2 receptor stimulation in mammalian cerebral cortex and hippocampus produces excitation by inhibition of Ca^{2+}-activated K conductances (Table 16-1). This effect resembles that produced by activation of β-adrenergic receptors in these areas and both are mediated by increases in the cAMP-PKA pathway. H_2 receptor activation also facilitates depolarization by enhancing HCN current, a cation channel activated by hyperpolarization (Haas & Panula, 2003; Haas et al., 2008). Although most of H_2 receptor signaling is therefore excitatory, H_2 receptors on hippocampal interneurons can also dampen maximum firing rates by inhibiting Kv3 channels (Atzori et al., 2000).

H_3 receptors are a family of GPCRs produced by gene splicing and linked to $G_{i/o}$

Although the genes encoding the H_1 and H_2 receptors have been known since 1991, this information did not help to identify the gene encoding the third HA receptor. This new histamine receptor was identified by pharmacological means in 1983 by Arrang and colleagues (Arrang et al., 1983) and has for many years been regarded as an interesting drug target for CNS diseases. The molecular identity of the H_3 receptor remained unknown until 1999, when, in a search for orphan GPCRs, a GPCR-related expressed sequence tag was identified *in silico* and used to clone a full-length human cDNA (Lovenberg et al., 1999). The cDNA contained an open reading frame of 445 amino acids with an aspartate residue in TM3 (Fig. 16-4). Such a residue is highly conserved in the family of biogenic amine receptors and was the first clue that the cDNA might encode for a new histamine receptor. The H_3 receptor protein shows very low homology with the H_1 and H_2 receptors (only to 22% and 20% respectively) or other GPCRs, explaining why the H_3 receptor gene was not cloned by homology screening with H_1– or H_2–receptor-specific probes. Currently, the rat, guinea pig, mouse and monkey cDNAs have been cloned (Hancock et al., 2003).

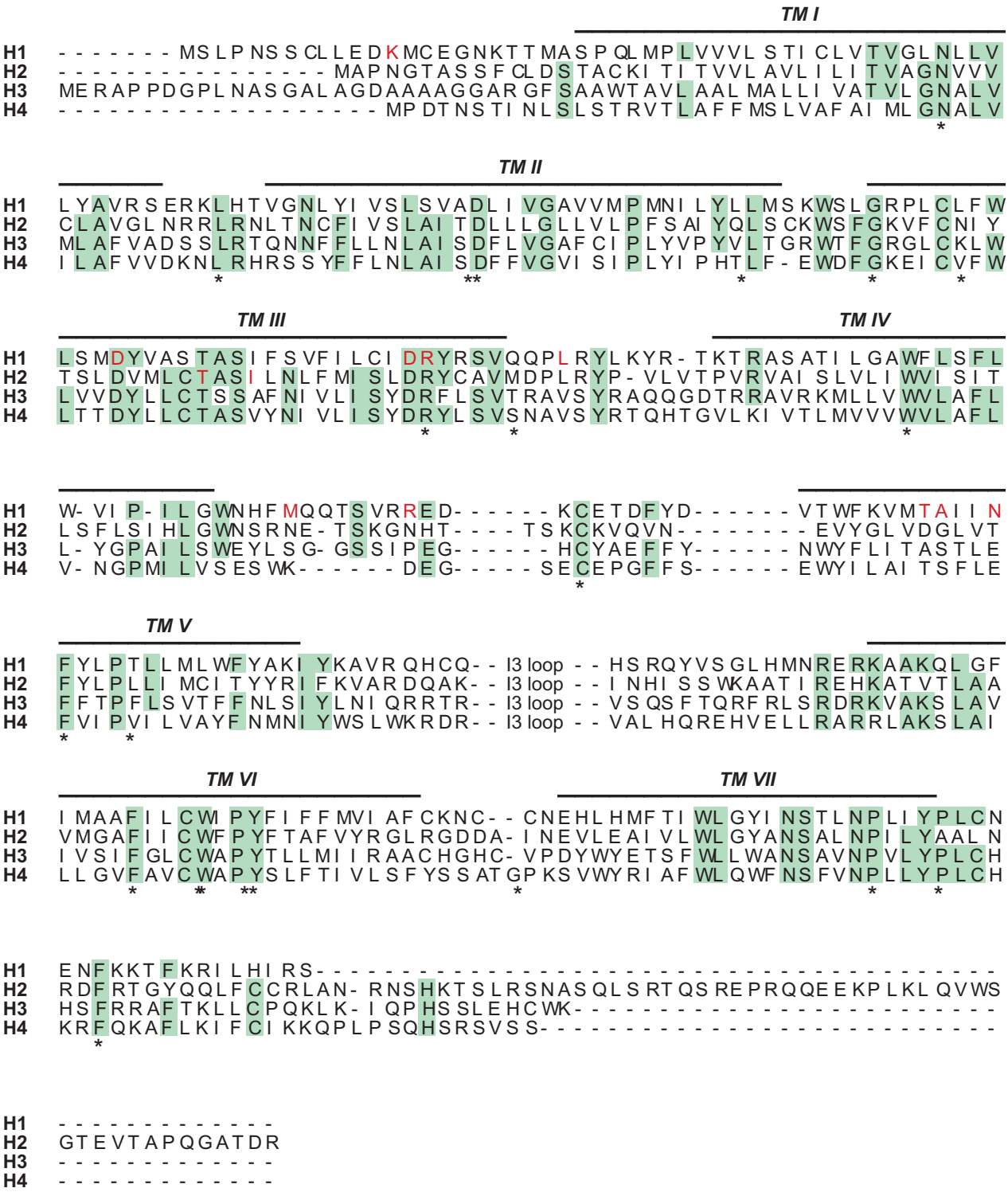

FIGURE 16-4 **Amino acid sequence alignment of the four human HA receptors.** The figure was produced using ClustalX (see http://www.clustal.org/). For ease of presentation, portions of the third intracellular loops (i_3) have been omitted. The green shaded areas indicated at least 75% conservation between subtypes. The asterisks indicate amino acid conservation with the rhodopsin sequence. Residues in red have been mutated and studied for their functional role in receptor function (ligand binding, signaling, glycosylation, phosphorylation), as indicated in the tiny GRAP/GPCRDB database (see also http://tinyGRAP.uit.no/). Above the sequences the putative transmembrane domains (TM) are indicated.

H_3 receptor gene splicing

The H_3 receptor gene from several species contains at least three introns (Fig. 16-5). Consequently, various isoforms have been identified for the human, rat and guinea pig H_3 receptor as a result of alternative splicing (Hancock et al., 2003). Alternative splicing of the third intron results in H_3 receptor isoforms that contain different deletions in the third intracellular i_3 loop. The i_3 loop is known to be important for the GPCR signaling, and indeed significant differences have in this respect been reported for the some of the isoforms (see below). Currently, at least 20 different human H_3 receptor isoform mRNAs have been identified as a result of various alternative-splicing events. However, functional characteristics and detailed information on their localization and relative abundance have been reported for only a small number of the isoforms (Hancock et al., 2003).

H_3-linked intracellular messengers

Although the H_3 receptor was initially identified by pharmacological means, detailed information on this receptor's transduction mechanisms was only obtained after the cloning of its cDNA. A pertussis toxin–sensitive inhibition of cAMP accumulation in response to H_3 agonists has been observed in a variety of transfected cells, indicating that the H_3 receptor negatively regulates adenylate cyclase activity via $G_{i/o}$ proteins (Fig. 16-6). The H_3-mediated regulation of HDC activity is also controlled via the cAMP-adenylate cyclase-PKA pathway (Gomez-Ramirez et al., 2002). The H_3 receptor has also been reported to activate the MAPK pathway in both transfected cells and rat brain (Drutel et al., 2001; Giovannini et al., 2003). Hippocampal administration of a mitogen activated protein kinase (MAPK) inhibitor demonstrated that the MAPK activation in CA3 pyramidal cells is important for H_3 receptor-induced memory retention (Giovannini et al., 2003).

In transfected cells, H_3 receptor-mediated activation of $G_{i/o}$ proteins has also been reported to modulate arachidonic acid release (Morisset et al., 2000) and the Na^+/H^+ exchanger (Silver et al., 2001), and to inhibit Ca^{2+} influx and exocytosis of [^{3}H] noradrenaline from transfected SH-SY5Y-H_3 cells (Silver et al., 2002; Bongers et al., 2007). The inhibition of Ca^{2+} influx may be particularly relevant in view of the known physiological function of the brain H_3 receptor. In transfected cells, the H_3 receptor modulates also the activity of the Akt/Glycogen synthase kinase 3β (GSK-3β) axis both in a constitutive and in an agonist-dependent fashion. H_3 receptor stimulation with the H_3 agonist immepip induces the phosphorylation of both Ser473 and Thr308 on Akt, a serine/threonine kinase that is important for neuronal development and function (Bongers et al., 2007). Moreover, phosphorylation of the Akt/GSK-3β can be observed in primary rat cortical neurons and rat striatal slices. In primary rat cortical neurons, the modulation of the Akt/GSK-3β pathway is implicated in an H_3 receptor mediated protection against neurotoxic insults (Mariottini et al., 2009).

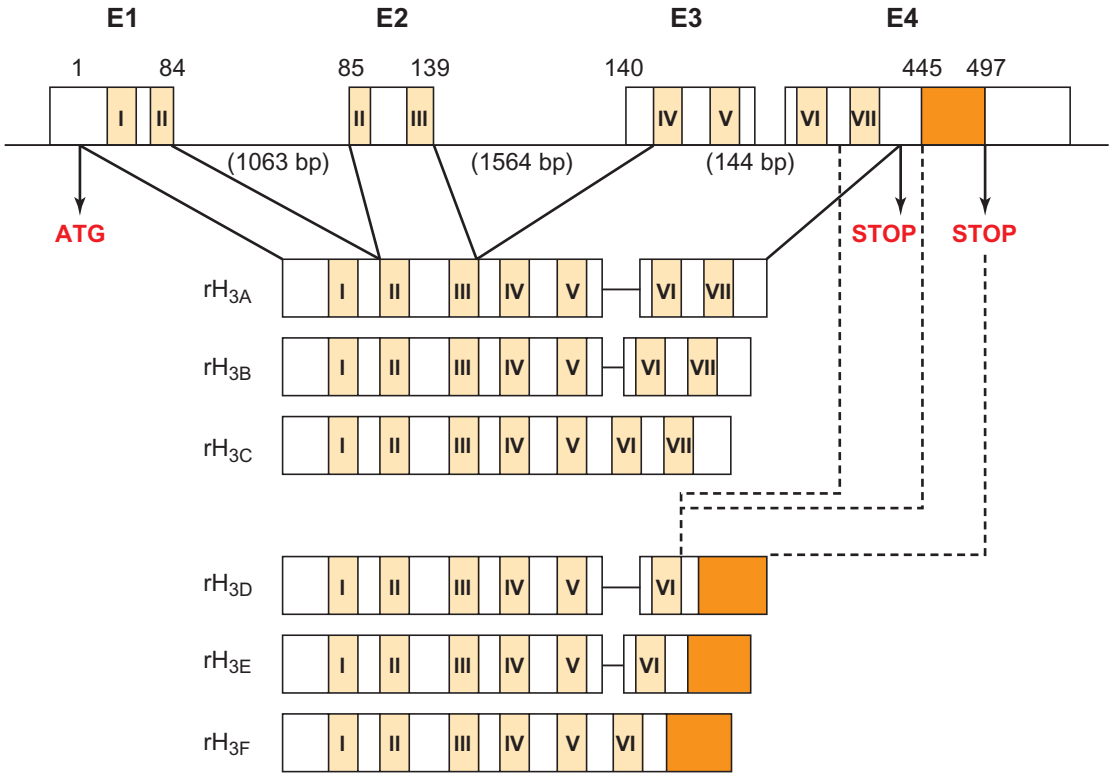

FIGURE 16-5 **Isoforms of the rat H_3 receptor.** The genomic structure of the receptor (top) shows four exons (boxes E1–E4) and three introns (bp sizes are in parentheses). Peptide sequences that correspond to translated TM regions are labeled with roman numerals (I–VII). An alternatively spliced region (orange box) is depicted between the stop sequences. Six isoforms of the receptor (labels are on the left) result from alternative splicing.

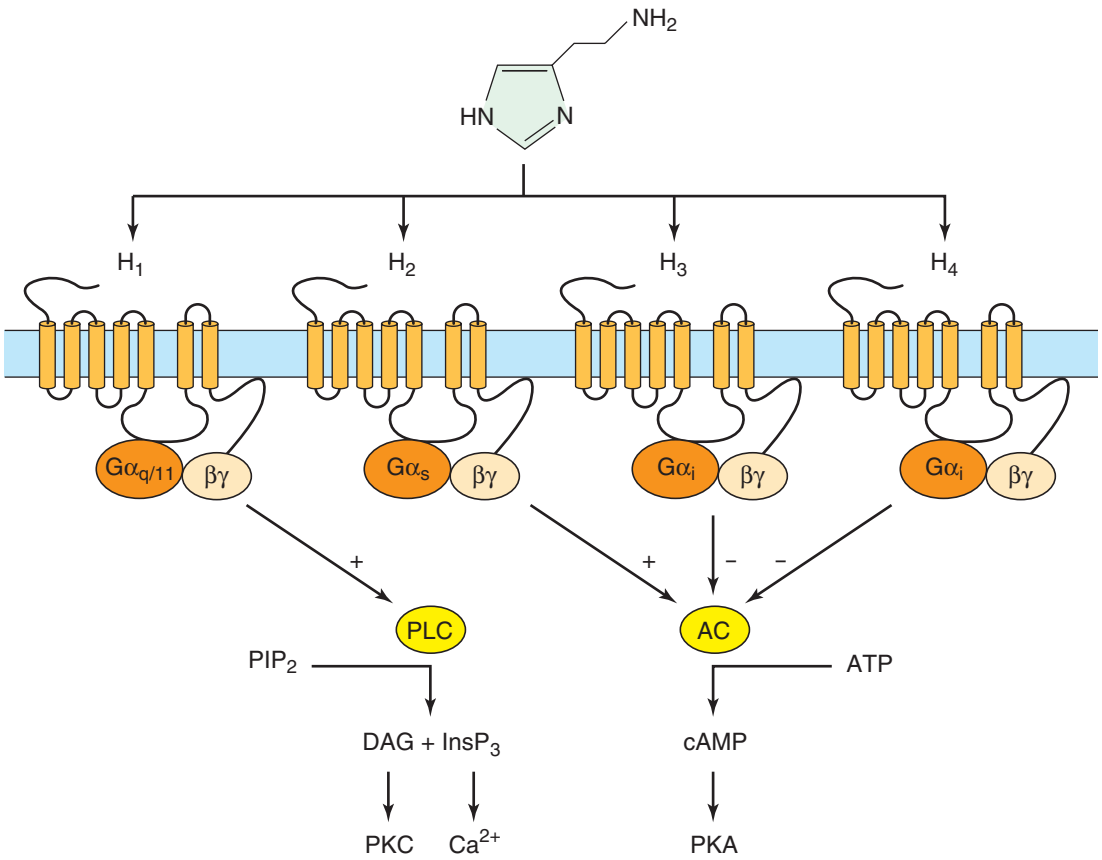

FIGURE 16-6 **Main signaling pathways for histamine receptors.** Histamine can couple to a variety of G-protein-linked signal transduction pathways via its four different receptors. The H_1 receptor activates the phosphoinositide turnover via $G_{q/11}$ proteins. The other receptors either positively (H_2 receptor) or negatively (H_3 and H_4 receptor) regulate adenylyl cyclase activity via G_s and $G_{i/o}$ protein activation respectively. Several additional signaling pathways have been described that are not shown. Abbreviations: PIP_2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic AMP; PKC, protein kinase C; PKA, protein kinase A.

At present it is not known if all H_3 receptor isoforms similarly activate the wide array of signaling pathways. In transfected cells, the rat $H_3(413)$ and $H_3(397)$ isoforms both inhibit adenylate cyclase more efficiently than does the full-length rat H_3 receptor isoform (445 amino acids), but the former are less efficient in activating the MAPK pathway. Much less information is available for the human H_3 receptor isoforms, but shorter isoforms seem to couple more efficiently to $G_{i/o}$-proteins to inhibit cAMP production in transfected cells (Hancock et al., 2003).

Constitutive H_3 receptor activity

In recent years it has become apparent that GPCRs can signal without the presence of the agonist, a phenomenon referred to as constitutive activity. Many GPCR antagonist ligands are able to reduce this agonist-independent signaling, an effect known as inverse agonism. All human histamine receptors have now been reported to show constitutive activity (Morisset et al., 2000; Alewijnse et al., 1998; Bakker et al., 2000; Morse et al., 2001). Moreover, well-known therapeutics such as cetirizine, loratadine, epinastine, cimetidine and ranitidine act as inverse agonists *in vitro* at constitutively active H_1 or H_2 receptors.

The H_3 receptor is one of the few examples of a GPCR showing a high level of constitutive activity in physiologically relevant systems. Whereas almost all of the findings on constitutively active GPCRs have been obtained with transfected cells that express very high receptor densities, experiments performed *in vivo* have shown that the brain H_3 receptor spontaneously signals in the absence of endogenous histamine. Thus, constitutively active H_3 receptors inhibit histaminergic (and possibly other) neuronal activity and this activity can be inhibited by a structurally diverse set of inverse agonists, thereby increasing neuronal activity (Morisset et al., 2000; Wieland et al., 2001). H_3 receptor signaling (both agonist-activated and agonist-independent) occurs through $G_{i/o}$-linked inhibition of high voltage–activated calcium conductances (Table 16-1; Haas & Panula, 2003).

H_4 receptors are very similar to H_3 receptors in gene structure and signal transduction, but show limited expression in the brain

The H_4 receptor gene was identified in 1999 as a direct consequence of the Human Genome Project. Use of the human H_3

receptor sequence led to the identification of a related orphan GPCR. Heterologous expression of the gene identified the orphan as a new member (H_4) of the histamine receptor family (Hough, 2001; Oda et al., 2000). The human H_4 receptor exhibits an exon/intron organization very similar to that of the H_3 receptor and the occurrence of isoforms can therefore be expected, but functional 7TM isoforms have so far not been reported.

Initially, the H_4 receptor mRNA was found in eosinophils, T-lymphocytes, neutrophils, mast cells, bone marrow, spleen, heart, lung and kidney, whereas expression in the brain was initially hard to detect. This expression profile has led to the suggestion that this new histamine receptor is an interesting target for the regulation of immune function. More detailed studies have now revealed transcripts of H_4 receptor in several regions of the human CNS, including spinal cord, hippocampus, cortex, thalamus and amygdala, with the highest levels of H_4 receptor mRNA in the spinal cord. Immunohistochemical analysis revealed H_4 receptor expression in the human cortex and mouse thalamus, hippocampus, cortex and spinal cord (Connelly et al., 2009).

H_4-linked intracellular messengers

Like the H_3 receptor, the H_4 receptor couples primarily to pertussis toxin–sensitive $G_{i/o}$ proteins. In transfected cells, activation of the H_4 receptor leads to a $G_{i/o}$ protein–mediated inhibition of forskolin-stimulated adenylate cyclase activity, [^{35}S]GTPγS binding, and activation of MAP kinase. Moreover, in eosinophils and mast cells, a pertussis toxin–sensitive calcium mobilization and chemotaxis have also been reported. The H_4 receptor can also couple to the relatively promiscuous G-proteins $G_{\alpha 15}$ and $G_{\alpha 16}$, leading to a stimulation of calcium mobilization. In view of the high expression of both the H_4 receptor and $G_{\alpha 15}$ and $G_{\alpha 16}$ proteins in cells of the immune system, this pathway could represent an important physiological second messenger system. In neurons of the mouse somatosensory cortex a hyperpolarization by H_4 receptor activation has been reported (Connelly et al., 2009).

Histamine can modify ionotropic transmission

Although known receptors for histamine in mammals are all coupled to G proteins, two histamine-operated chloride channels, *hcl*A and *hcl*B, have been cloned from the fruit fly *D. melanogaster* (Gisselmann et al., 2002; Pantazis et al., 2008). Both have the predicted four transmembrane–spanning regions and two cysteine bridges typical of all glycine and GABA-operated chloride channels. These channels are most closely related in structure to human glycine receptors but also bear resemblance to GABA- and glutamate-receptor-channel complexes. They are activated by micromolar concentrations of histamine and are blocked by high concentrations of some H_1 and H_2 antagonists. There is strong evidence that histamine activation of *hcl*A mediates the photoreceptor transmission in insect vision. Although native mammalian homologs of these channels have not been found, there is substantial recent evidence for their existence in the mammalian brain (Lee et al., 2004). Histamine also potentiates N-methyl-D-aspartate (NMDA) receptors through an allosteric interaction (Haas et al., 2008), likely at the polyamine binding site on NR1/NR2B subunits. It is sensitive to pH and opposite to the proton action on this receptor channel. Endogenous histamine could act at this site to facilitate the induction of long-term potentiation and learning (Brown et al., 2001). Additional histamine receptors may still be discovered.

HISTAMINE ACTIONS ON THE NERVOUS SYSTEM

Histamine in the brain may act as both a neuromodulator and a classical transmitter

Histaminergic transmission utilizes a variety of signaling mechanisms in the brain. Like all the other biogenic amines, histamine is mostly released nonsynaptically at some distance from the target membranes and receptors, implying wide diffusion of the 'neuromodulator.' Nevertheless, all these amines are now usually referred to as transmitters. Activation of the small number of TM cells releases histamine, which subsequently increases excitability in target regions distributed widely throughout the brain (Wada et al., 1991; Haas et al., 2008). Such a system is consistent with the characteristics of known histamine receptors, which function through 'slow' transmission mechanisms requiring the production of intracellular second messengers (Table 16-1, see Chap.12 for overview). However, histamine provides fast neurotransmission in mollusks and arthropods as a ligand of a chloride channel receptor complex. Electrical stimulation of the TM cells evokes fast excitatory postsynaptic potentials in phasically firing supraoptic neurons, effects that are mimicked by the application of histamine (Haas et al., 2008). It increases a chloride conductance in the thalamus by a mechanism that may be related to H_2 receptors, or to the not-yet-characterized mammalian histamine ion channel (Lee et al., 2004). Thus histamine, like serotonin (see Chap.15) can activate both ligand-operated channels and receptors linked to second messengers. Histamine gates homomultimeric channels composed of $GABA_A$ receptor β- subunits expressed in *Xenopus* oocytes, in which GABA is only a weak partial agonist. In some heteromultimeric channels histamine potentiates the GABA response but does not act as an agonist (Haas et al., 2008).

Histaminergic neurons are mutually connected with other neurotransmitter systems

A number of other transmitter systems can interact with histaminergic neurons. The H_3 receptor functions not only as an autoreceptor but also as an inhibitory heteroreceptor located on the axon varicosities of multiple glutamatergic, aminergic and other neurons (Fig. 16-7). Thus, activation of H_3 receptors decreases the release of acetylcholine, dopamine, norepinephrine, serotonin and certain peptides. Histamine can also increase the activity of these systems through H_1 and/or H_2 receptors, located on the neuronal somata and dendrites. Histaminergic neurons are excited by glutamatergic afferents and applied glutamate through AMPA and NMDA receptors (Yang & Hatton, 1997) by serotonin, dopamine,

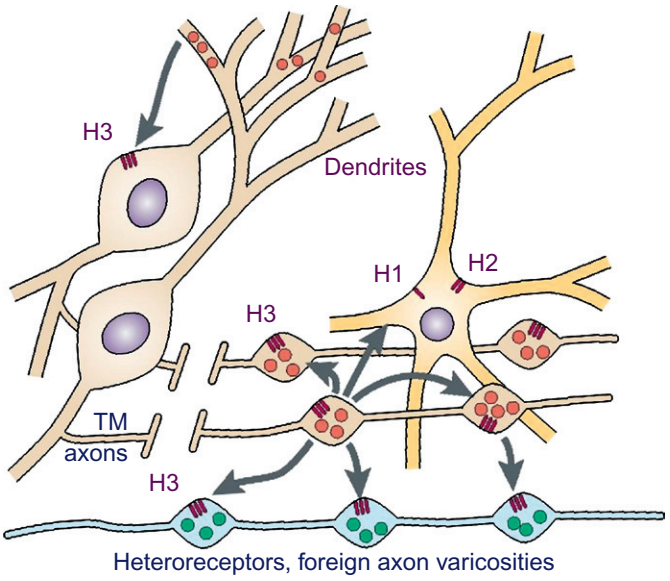

FIGURE 16-7 The targets of histaminergic neurons in the brain. H_3 receptors are located in the outer membranes of histaminergic neurons, their cell bodies, dendrites and axons (autoreceptors), as well as on the axonal varicosities of other neurons (heteroreceptors on glutamatergic, cholinergic, catecholaminergic, serotonergic, GABAergic, peptidergic cells). H_1 and H_2 receptors are found on target cell membranes. Histamine is released from dendritic and axonic vesicles. Modified from *Nature Reviews Neuroscience* 4:121–130, Haas et al., The role of histamine and the tuberomamillary nucleus in the nervous system. Copyright 2003, Macmillan Magazines Ltd.

acetylcholine, purines and peptides like the orexins (Haas et al., 2008). Noradrenaline, adenosine and morphine have no direct action but suppress GABAergic inhibition of TMN neurons. This inhibition is their most important inhibitory input coming from the preoptic area to suppress the waking activity of the TM neurons during non-REM and REM sleep. Further inhibitory actions have been described for galanin and nociceptin (orphanin FQ) (Haas et al., 2008).

Histamine functions in the nervous system

Most of the suspected physiological roles for histamine are related to its ability to increase neuronal excitability (Haas et al., 2008; Haas & Panula, 2003; Hough & Leurs, 2002). Pharmacological inhibition of TM activity induces sedation, and mutant mice lacking histamine or the H_1 receptor are sleepy and show defective locomotor and exploratory behaviors (Inoue et al., 1996). All available evidence from several species shows that histaminergic neurons, when activated, increase wakefulness and induce electrographic arousal (Takahashi et al., 2006). TM cells fire exclusively during waking and are inhibited by GABAergic sleep-active neurons in the preoptic area; neuronal histamine release is consequently much higher during wakefulness. H_1 receptor–mediated excitation in the ventrolateral hypothalamus, the (cholinergic) basal forebrain (Cecchi et al., 2001), the catecholaminergic and the serotonergic nuclei, and the thalamic relay neurones (Uhlrich et al., 2002) as well as the cerebral cortex and the hippocampus, are orchestrated to produce the cortical activation that underlies consciousness and wakefulness (Lin et al., 2011). Histamine and the orexins, located in the neighboring perifornical area, are the most important regulators of the waking state, with histamine being more responsible for the cognitive aspects and the orexins concerned instead with the behavioral and motor aspects (Anaclet et al., 2009).

On the other hand, histamine reduces seizure activity through H_1-receptors, an effect that can be explained by the excitation observed on inhibitory interneurons and the direct inhibition of pyramidal cells (Haas et al., 2008). H_1-receptor antagonists can be proconvulsive in children and animals, and H_1 receptor numbers are increased in some types of human epileptic foci (Iinuma et al., 1993). H_3 antagonists increase seizure threshold in a variety of models, consistent with an elevation in neuronal histamine release. Centrally administered histamine agonists can also enhance learning and retention in laboratory animals (Giovannini et al., 2003; Passani et al., 2000; Dere et al., 2003).

Histamine is a powerful regulator of many hypothalamic functions concerned with the homoeostasis of the whole organism, the control of the endocrine (Knigge & Warberg, 1991) and the vegetative nervous systems, energy administration, temperature regulation and even breathing and blood pressure (Prast & Philippu, 1991). Histamine excites the neurons in the supraoptic and paraventricular nuclei that release the antidiuretic hormone (vasopressin) from their nerve endings in the neurohypophysis (Haas et al., 2008). Hypothalamic histamine, through both H_1 and H_2 receptors, also participates in the physiological regulation of oxytocin, prolactin, adrenocorticotrophic hormone (ACTH) and β-endorphin release (Knigge & Warberg, 1991). Neuronal histamine is also an effective modulator of both food and water intake (Onodera et al., 1994). Histamine and compounds that increase extracellular histamine concentrations are powerful suppressants of food intake, whereas H_1 receptor antagonists (e.g., many neuroleptics) lead to obesity. An action on the H_1 receptor in the ventromedial hypothalamus (VMH) seems to account for these effects (Ookuma et al., 1993). Evidence that histamine contributes to the physiological control of appetite includes findings with genetically obese Zucker rats, which have very low concentrations of hypothalamic histamine. Furthermore, several studies suggest that leptin, the most powerful physiological suppressant of appetite, signals through histaminergic activation of H_1 receptors. Orexin excites histaminergic neurons. Histamine is also a powerful dipsogen (an agent that induces drinking), whether administered systemically or directly into the hypothalamus. Multiple hormonal and neuronal mechanisms may contribute to these effects.

Histamine also induces antinociceptive (pain-relieving) responses in animals after microinjection into several brain regions (Hough & Rice, 2011). H_1 and H_2 mechanisms are significant, and both neuronal and humoral mechanisms may be involved. Brain H_2 receptors appear to mediate some forms of endogenous analgesic responses, especially those elicited by exposure to stressors. Many of the modulatory actions of histamine discussed above appear to be activated as part of stress responses. For reasons that remain unclear, histamine releasers, such as thioperamide, show only mild, biphasic antinociceptive actions, even though histamine is a potent and

effective analgesic substance. Outside the brain, both H_1 and H_3 receptors exist on certain types of sensory nerves, and activation of these receptors promotes and inhibits, respectively, peripheral nerve transmission related to pain and/or inflammation (Raffa, 2001). There are specific nerve endings for itching that are activated by histamine (Schmelz, 2002). The pain and itch caused by nettles is mediated by histamine located in the spines on the leaves.

Histamine may contribute to nervous system diseases or disorders

There are significant changes in the brain histamine system in several neurological diseases, such as multiple sclerosis, Alzheimer's disease, Down syndrome and Wernicke's encephalopathy (Haas & Panula, 2003; Haas et al., 2008; Langlais et al., 2002; Onodera et al., 1994). In some of these cases, there are clear changes in the number or morphology of histaminergic neurons. Whether from neurons or mast cells, histamine may participate in these processes by contributing to changes in vascular function, blood–brain barrier and/or immune activity. The ability of histamine to enhance excitatory transmission at NMDA receptors (discussed above) could explain its neurotoxic actions (Langlais et al., 2002). However, increases in neuronal histamine do not always enhance brain damage; histamine seems to exert a protective effect in some models of cerebral ischemia. Alterations in brain histamine content or dynamics may also be important for cognitive changes resulting from liver disease or histidinemia (an inborn error of histidine metabolism). In addition, histaminergic neurons are activated by vestibular disturbances, leading to the release of histamine in brainstem emetic centers. Thus, neuronal histamine may be one mediator of motion sickness (Takeda et al., 1993).

Tourette's syndrome is a common developmental neuropsychiatric disorder characterized by chronic motor and vocal tics. The occurrence of Tourette's syndrome in subjects displaying a functional mutation in the gene encoding L-histidine decarboxylase, the rate-limiting enzyme in histamine biosynthesis, points to a role for histaminergic neurotransmission in the mechanism and modulation of Tourette's syndrome and tics (Ercan-Sencicek et al., 2010).

Although histamine is not stored in neurons outside the central nervous system, mast cell–derived histamine can modify peripheral sensory nerve function. Both acute and chronic pain states can result from inflammation or peripheral nerve cell injury, and there is substantial evidence that mast cell histamine participates in these disorders.

SIGNIFICANCE OF BRAIN HISTAMINE FOR DRUG ACTION

Many clinically available drugs that modify sleep–wake cycles and appetite act through the histaminergic system

The role of histamine in the brain was initially acknowledged only for the sedative or orexigenic actions of brain-penetrating antagonists of the H_1 receptor, commonly used in allergic disorders such as hay fever, or psychoactive compounds including antidepressants and typical and atypical antipsychotic medications. These undesired side effects are essentially mediated by the blockade of brain H_1 receptors that are crucial for the regulation of the sleep/wake pattern and the diurnal rhythm of food intake. Nearly all of the over-the-counter sleep aids are brain-penetrating antagonists of the H_1 receptor (e.g., chlorpheniramine and diphenhydramine), although their use is limited as they display long half-lives and antimuscarinic effects such as constipation, dry mouth and blurred vision. These limitations have prompted the synthesis of more selective H_1-receptor antagonists with optimized pharmacokinetic properties. Nevertheless, classic H_1 antagonists are still used for the treatment of motion sickness and Ménière's disease, a related disorder of the inner ear. There are also medications used to produce the opposite effect (i.e., increased wakefulness), but H_1 agonists are not used to treat hypersomnia or eating disorders, as all brain-penetrating compounds have unacceptable peripheral side effects.

Drugs that modify pain perception act in part through the histaminergic system

Although pain-relieving opioid drugs such as morphine initiate many neurochemical changes, the activation of neuronal histamine release by these agents and the subsequent stimulation of brain H_2 receptors are critical for the mechanism of action of these compounds (Gogas et al., 1989; Eriksson et al., 2000). Stress responses also can contribute to opioid analgesia, and histaminergic neurons appear to mediate the stress-induced potentiation of morphine antinociception. Although no pain-relieving drugs have been developed based on H_2 receptors, a family of novel analgesics has been discovered from drugs related to cimetidine (an H_2 antagonist) and burimamide (a drug with both H_2 and H_3 properties). Thus far, these improgan-like drugs have been used only as research tools. Outside the brain, H_1 receptors on sensory nerve fibers are activated during some kinds of pain and inflammation, and H_1 antagonists are used for their anti-inflammatory and analgesic profiles (Raffa, 2001). By an opposing mechanism, H_3 agonists reduce pain transmission evoked by chemical and mechanical stimuli (Hough & Rice, 2011).

The H_3 receptor is an attractive target for the treatment of several CNS diseases

The H_3 receptor is not only an autoreceptor, but it also controls release of other neurotransmitters, including 5-HT, acetylcholine, dopamine and noradrenaline (Fig. 16-7; Haas et al., 2008). These features render it a very attractive therapeutic target for CNS disorders, as agents with multiple and complementary modes of action are more likely to show broad-based efficacy against core and co-morbid symptoms. Several H_3 receptor antagonists are in clinical trials for the treatment of narcolepsy, cognitive impairments associated with Alzheimer's disease, Parkinson's disease, schizophrenia and attention deficit hyperactivity disorder (ADHD) (Benarroch, 2010). A striking property of H_3 receptors is their high degree

of constitutive activity *in vivo* (Morisset et al., 2000). This discovery is important for drug development, since the ability to compete with constitutively active H_3 receptor states (inverse agonism) has important therapeutic implications.

H_3 antagonists are effective in the treatment of sleep disturbances (Lin et al., 2011). Primary narcolepsy, a disorder characterized by excessive daytime sleepiness, cataplexy, and narcoleptic episodes, as well as sleepiness of various causes, are currently treated mainly by wake-promoting compounds such as modafinil or psychostimulants, like amphetamine, that act through the dopaminergic system. Despite their potent arousal effects, these compounds presumably do not activate histaminergic mechanisms, as their effects are preserved in HDC-KO mice. The brain H_3 receptor is currently the most promising target to treat hypersomnia, as its blockade increases histamine release, which stimulates postsynaptic H_1 receptors. Indeed, H_3 antagonists show a remarkable wake-promoting effect in experimental animals, and clinical studies confirm the validity of this drug class for treating somnolence and vigilance deficiency of diverse pathological origins (Lin et al., 2008). All these compounds show a better pharmacological profile than other psychostimulants, because unlike amphetamines, caffeine or modafinil, they do not provoke rebound effects or behavioral excitation.

H_3 antagonists may also present unique therapeutic options for the treatment of cognition disorders, the dreadful hallmarks across a broad range of neuropsychiatric diseases in patients of all ages. Drugs currently employed have modest efficacy, and side effects are common. Pharmacological blockade of H_3 receptors exerts procognitive effects in a variety of preclinical models related to ADHD, Alzheimer's disease and schizophrenia (Brioni et al., 2011; Passani et al., 2004). These encouraging results have prompted clinical trials testing the procognitive properties of H_3 antagonists in these diseases. Current treatment strategies are focused on a single neurotransmitter system (e.g., dopaminergic stimulants for ADHD, cholinesterase inhibitors for AD), although multiple neurotransmitter systems and brain circuits are presumably involved. H_3 receptor blockade can elevate concentrations of histamine, acetylcholine, dopamine, serotonin and noradrenaline in the cortex and may offer a better target for affecting cognitive processes, which often rely on the integration of multiple neurotransmitter systems. It is noteworthy that H_3 antagonists do not increase dopamine release in the striatum and nucleus accumbens, a favorable attribute for clinical use in light of extrapyramidal side effects and addiction liabilities.

Drugs that act on the histaminergic system are also promising candidates for the treatment of obesity, epilepsy and

DAYTIME SLEEPINESS AND NARCOLEPSY

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At the end of the First World War a disastrous influenza epidemic took a higher toll in human lives than the war itself. Constantin von Economo described sleep disturbances in some of the victims associated with characteristic lesions in the hypothalamus (Von Economo, 1930): hypersomnia "Encephalitis lethargica" was associated with destruction of neurons in the posterior hypothalamus comprising, as we know now, the histamine and the orexin/hypocretin neurons. There were also cases of fatal insomnia associated with lesions in the preoptic area, which contains sleep-active GABAergic neurons that inhibit the waking systems. This inhibition of the wake-active neurons is enhanced by barbiturates, benzodiazepines, ethanol and general anesthetics like propofol. The drowsiness (and weight gain) caused by antihistamines and by many drugs used in the therapy of neuropsychiatric disorders is attributed to the block of histamine H1 receptors (Lin et al., 2011). Simple daytime sleepiness such as brief sleep attacks while driving is very common and often has serious consequences. More spectacular and much rarer is narcolepsy/cataplexy, which features, in addition to irresistible daytime sleep attacks, sudden onset of REM sleep with paralysis upon waking (cataplexy) and hypnagogic hallucinations (dreams before losing consciousness) (Mignot & Nishino, 2005). Most narcoleptic patients suffer from a likely autoimmune-induced loss of orexins/hypocretins from neurons in the periventricular area of the hypothalamus. Recent experimental data suggest that both the orexin/hypocretin and the histamine systems may be affected in full-blown narcolepsy with cataplexy (Anaclet et al., 2009).

Treatment of these ailments with, e.g., amphetamines, GHB and antidepressants is so far not satisfactory (Mignot & Nishino, 2005). With the recognition of the major role of the histamine system in waking and the widespread innervation of other systems involved in sleep-wake control it became obvious that an enhancement of histaminergic activity and the release of other transmitters, including glutamate, acetylcholine, serotonin and the catecholamines, would be an adequate strategy. This is possible through blocking the H3 autoreceptors and heteroreceptors and thus disinhibiting transmitter release. Several H3 receptor antagonists/partial agonists with a wide range of indications in neuropsychiatric disorders are on their way to the clinic at present for this purpose (Lin et al., 2011).

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neurodegenerative disorders. H_1 receptor antagonists increase food consumption and body weight, whereas activating H_1 receptors suppresses food intake, and increasing brain histamine availability under H_3 receptor antagonists induces weight loss (Passani et al., 2011). Although H_3-receptor antagonists did not induce any significant weight change in patients enrolled in clinical trials aimed at testing their efficacy in narcolepsy or ADHD, these compounds may turn out to be effective in treating specific eating disorders. Preclinical data suggest that H_3 antagonists might be useful for the treatment of alcoholism (Nuutinen et al., 2010) as well as epilepsy (Benarroch, 2010). Histamine is also involved in the pathology of multiple sclerosis and its murine model, experimental autoimmune encephalomyelitis, and its role in neuroprotection is currently under consideration.

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