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HISTAMINE

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In a certain way, histaminergic systems have had a great, although indirect, historical importance in the development of neuropsychopharmacology. Indeed, the discovery of both the neuroleptic agents and the tricyclic antidepressant drugs in the 1950s was derived from the clinical study of behavioral actions of "antihistamines," a class of antiallergic drugs now designated *H_1-receptor antagonists.*

Nevertheless, the histaminergic neuronal system in the brain, although already understood by the mid-1970s, has remained largely unexploited in drug design. Thus, only the traditional brain-penetrating H_1-receptor antagonists, used as over-the-counter sleeping pills, are known to interfere with histaminergic transmissions in the central nervous system (CNS). This situation contrasts with the emergence, in the 1990s, of detailed knowledge of the system that revealed that it shares many biological and functional properties with other aminergic systems overexploited in CNS drug design.

Histamine and its receptors in the brain have been the subject of two comprehensive reviews (1,2). Therefore, to limit the length of the present chapter, we have deliberately elected to summarize the detailed information that can be found in these reviews and have added only more recent information and major references.

ORGANIZATION OF THE HISTAMINERGIC NEURONAL SYSTEM

One decade after the first evidence by Garbarg et al. of an ascending histaminergic pathway obtained by lesions of the medial forebrain bundle (3), the exact localization of corresponding perikarya in the posterior hypothalamus was revealed immunohistochemically, and the distribution, morphology, and connections of histamine and histidine decarboxylase-immunoreactive neurons were determined. Data were comprehensively reviewed (4–7), and they are summarized only briefly here.

All known histaminergic perikarya constitute a continuous group of mainly magnocellular neurons (about 2,000 in the rat), located in the posterior hypothalamus and collectively named the *tuberomammillary nucleus* (Fig.14.1). It can be subdivided into medial, ventral, and diffuse subgroups extending longitudinally from the caudal end of the hypothalamus to the midportion of the third ventricle. A similar organization was described in humans, except histaminergic neurons are more numerous (approximately 64,000) and occupy a larger proportion of the hypothalamus (8). Besides their large size (25 to 35 μm), tuberomammillary neurons are characterized by few thick primary dendrites, with overlapping trees, displaying few axodendritic synaptic contacts. Another characteristic feature is the close contact of dendrites with glial elements in a way suggesting that they penetrate the ependyma and come in close contact with the cerebrospinal fluid, perhaps to secrete or receive still unidentified messengers. Neurons expressing mRNAs for histidine decarboxylase (EC 4.1.1.22), the enzyme responsible for the one-step histamine formation in the brain (2), were found by *in situ* hybridization in the tuberomammillary nucleus, but not in any other brain area (9). Tuberomammillary neurons possess the vesicular monoamine transporter 2 (10), which accounts for the histamine-releasing effect of reserpine (2).

The histaminergic neurons are characterized by the presence of an unusually large variety of markers for other neurotransmitter systems: glutamic acid decarboxylase, the γ-aminobutyric acid (GABA)–synthesizing enzyme; adenosine deaminase, a cytoplasmic enzyme possibly involved in adenosine inactivation; galanin, a peptide co-localized with all other monoamines; (Met^5)enkephalyl-Arg^6Phe^7, a product of the proenkephalin A gene; and other neuropeptides such as substance P, thyroliberin, or brain natriuretic peptide. Tuberomammillary neurons also contain monoamine oxidase B, an enzyme responsible for deamination of telemethylhistamine, a major histamine metabolite in brain. Finally, a subpopulation of histaminergic neurons is able to take up and decarboxylate exogenous 5-hydroxytryptophan,

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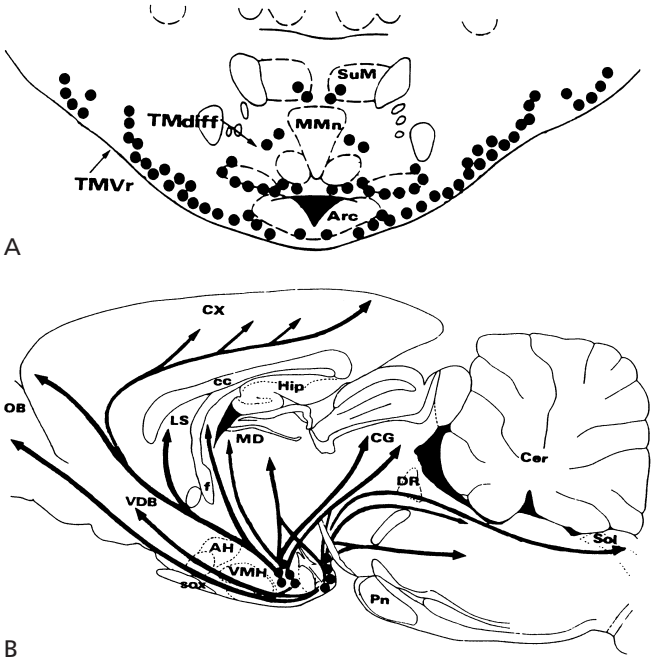

FIGURE 14.1. Localization of histaminergic perikarya *(closed circles)* in tuberomammillary nucleus and disposition of main histaminergic pathways *(arrows)* in rat brain. **A:** Frontal section of the caudal hypothalamus. **B:** Sagittal section of the brain. AH, anterior hypothalamic area; Arc, arcuate nucleus; cc, corpus callosum; Cer, cerebellum; CG, central gray; CX, cerebral cortex; DR, dorsal raphe nucleus; f, fornix; Hip, hippocampus; LS, lateral septum; MD, mediodorsal thalamus; MMn, medial mammillary nucleus median part; OB, olfactory bulb; Pn, pontine nuclei; Sol, nucleus of solitary tract; Sox, supraoptic decussation; sum, supramammillary nucleus; TMdiff, tuberomammillary nucleus diffuse part; TMVr, ventral tuberomamillary subgroup rostral part; VDB, nucleus of vertical limb of diagonal band; VMH, ventromedial hypothalamic nucleus.

a compound that they do not synthesize, however (5). Discovering the functions of such a high number of putative cotransmitters in the same neurons remains an exciting challenge.

Like other monoaminergic neurons, histaminergic neurons constitute long and highly divergent systems projecting in a diffuse manner to many cerebral areas (Fig.14.1). Immunoreactive, mostly unmyelinated, varicose or nonvaricose fibers are detected in almost all cerebral regions, particularly limbic structures, and it was confirmed that individual neurons project to widely divergent areas. Ultrastructural studies suggest that these fibers make few typical synaptic contacts (6).

Fibers arising from the tuberomammillary nucleus constitute two ascending pathways: one laterally, through the medial forebrain bundle, and the other periventricularly. These two pathways combine in the diagonal band of Broca to project, mainly in an ipsilateral fashion, to many telencephalic areas, for example, in all areas and layers of the cerebral cortex, the most abundant projections being to the external layers. Other major areas of termination of these long ascending connections are the olfactory bulb, the hippocampus, the caudate putamen, the nucleus accumbens, the globus pallidus, and the amygdaloid complex. Many hypothalamic nuclei exhibit a very dense innervation, for example, the suprachiasmatic, supraoptic, arcuate, and ventromedial nuclei.

Finally, a long descending histaminergic subsystem also arises from the tuberomammillary nucleus to project to various mesencephalic and brainstem structures such as the cranial nerve nuclei (e.g., the trigeminal nerve nucleus), the central gray, the colliculi, the substantia nigra, the locus ceruleus, the mesopontine tegmentum, the dorsal raphe nucleus, the cerebellum (sparse innervation), and the spinal cord.

Several anterograde and retrograde tracing studies established the existence of afferent connections to the histaminergic perikarya, namely, from the infralimbic cortex, the septum-diagonal band complex, the preoptic region, the hypothalamus, and the hippocampal area (subiculum) (7, 11). Sleep-active GABAergic neurons in the ventrolateral preoptic nucleus provide a major input to the tuberomammillary nucleus (12,13). Histaminergic neurons also receive very dense orexin innervation originating from the lateral hypothalamus (14). Electrophysiologic studies provided evidence of inhibitory and excitatory synaptic control of tuberomammillary neuron activity by afferents from the diagonal band of Broca, the lateral preoptic area and the anterior lateral hypothalamic area (15). Projections from the brainstem to the tuberomammillary nucleus have also been demonstrated. Retrograde tracing studies combined with immunohistochemistry showed that monoaminergic inputs to the tuberomammillary nucleus originate mainly from the ventrolateral and dorsomedial medulla oblongata and from the raphe nuclei, with a low innervation originating from the locus ceruleus, the ventral tegmental area, and the substantia nigra (16).

MOLECULAR PHARMACOLOGY AND LOCALIZATION OF HISTAMINE RECEPTOR SUBTYPES

Three histamine receptor subtypes (H_1, H_2 and H_3) have been defined by means of functional assays, followed by design of selective agonists and antagonists and, more recently, cloning of their genes (1). All three belong to the superfamily of receptors with seven transmembrane domains (TMs) and coupled to guanylnucleotide-sensitive G proteins (Table 14.1). In addition, histamine affects the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor (17, 18).

Histamine H_1 Receptor

The H_1 receptor was initially defined in functional assays (e.g., smooth muscle contraction) and in the design of po-

TABLE 14.1. PROPERTIES OF THREE HISTAMINE RECEPTOR SUBTYPES

	H_1	H_2	H_3
Coding sequence	491 a.a. (bovine) 488 a.a. (guinea pig) 486 a.a. (rat)	358 a.a. (rat) 359 a.a. (dog, human, guinea pig)	445 a.a. (human) H_{3L} 445 a.a., H_{3S} 415 a.a. (guinea pig) H_{3L} 445 a.a., H_{3S} 413 a.a. (rat)
Chromosome localization	3p25	5	20qTEL
Highest brain densities	Thalamus Cerebellum Hippocampus	Striatum Cerebral cortex Amydgala	Striatum Frontal cortex Substantia nigra
Autoreceptor	No	No	Yes
Affinity for histamine	Micromolar	Micromolar	Nanomolar
Characteristic agonists	2-(3-Trifluoromethyl) histamine	Impromidine Sopromidine	(R)α-Methylhistamine Imetit
Characteristic antagonists	Mepyramine	Cimetidine	Thioperamide Ciproxifan
Radioligands	[^{3}H]Mepyramine [^{125}I]Iodobolpyramine	[^{3}H]Tiotidine [^{125}I]Iodoamino-potentidine	[^{3}H](R)α-Methylhistamine [^{125}I]Iodoproxyfan
Second messengers	Inositol phosphates (+) Arachidonic acid (+) cAMP (potentiation)	cAMP (+) Arachidonic acid (–) Ca^{++} (+)	cAMP (–) Inositol phosphates (–) Arachidonic acid (+) Ca^{++} (–)

tent antagonists, the so-called *antihistamines* (e.g., mepyramine), most of which display prominent sedative properties. Biochemical and localization studies of the H_1 receptor were made feasible with the design of reversible and irreversible radiolabeled probes such as [^{3}H] mepyramine, [^{125}I]iodobolpyramine, and [^{125}I]iodoazidophenpyramine (19,20).

Various intracellular responses were found to be associated with H_1-receptor stimulation: inositol phosphate release, increase in Ca^{2+} fluxes, cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate accumulation in whole cells and arachidonic acid release (1).

The deduced amino acid sequence of a bovine H_1 receptor was disclosed after expression cloning of a corresponding cDNA. The latter was based on the detection of a Ca^{2+}-dependent Cl^- influx into microinjected *Xenopus* oocytes. After the transient expression of the cloned cDNA into COS-7 cells, the identity of the protein as an H_1 receptor was confirmed by binding studies (21).

Starting from the bovine sequence, the H_1 receptor DNA was also cloned in the guinea pig (22), a species in which the pharmacology of the receptor is better established, as well as from several other species including humans (1). Although marked species differences in H_1-receptor pharmacology had been reported (2), the sequence homology between the putative TMs of the proteins is high (90%).

The "anatomy" of the H_1 receptor, with a long third intracellular domain and a short C-terminal tail, is similar to that of other receptors positively coupled to phospholipases A_2 and C. Amino acid sequence homology between the TMs of the H_1 and those of the muscarinic receptors (approximately 45%) is higher than between those of H_1 and H_2 receptors (approximately 40%). H_1-receptor antagonists often display significant antimuscarinic activity but only limited H_2-receptor–antagonist properties.

A single gene seems to encode the guinea pig H_1 receptor, and mRNAs of similar size were detected in brain areas and peripheral tissues (22).The structure of the human gene was disclosed (23). Like other receptors of this superfamily, it contains an intron in the 5′ flanking untranslated region, close to the translation initiation codon, but the translated region is intronless.

When stably expressed in transfected fibroblasts, the guinea pig H_1 receptor was found to trigger a large variety of intracellular signals involving or not coupling to pertussis toxin-sensitive G proteins (G_i or G_o), namely, Ca^{2+} transients, inositol phosphates, or arachidonate release (24). H_1 receptor stimulation potentiates cAMP accumulation induced by forskolin in the same transfected fibroblasts, a response that resembles the H_1 potentiation of histamine H_2- or adenosine A_2-receptor–induced accumulation of cAMP in brain slices. All these responses mediated by a single H_1 receptor were known to occur in distinct cell lines or brain slices, but they could have resulted from stimulation of isoreceptors.

Constitutive activity of the recombinant human H_1 re-

ceptor consisting in an agonist-independent increase in inositol phosphates accumulation in COS-7 cells was evidenced. Several H_1-receptor antagonists behaved as inverse agonists (i.e., reduced this constitutive activity), but the physiologic relevance of the process, such as in brain, was not established (25).

The H_1 receptor mediates various excitatory responses in brain (26). A reduction of a background leakage K^+ current was implicated in these responses, in cortical, striatal, and lateral geniculate relay neurons (27,28).

H_1-receptor distribution in the guinea pig brain was established autoradiographically using [^{3}H]mepyramine or the more sensitive probe [^{125}I]iodobolpyramine (20), and the information was complemented by *in situ* hybridization of the mRNA (22). For instance, the high density of H_1 receptors in the molecular layers of cerebellum and hippocampus seems to correspond to dendrites of Purkinje and pyramidal cells, respectively, in which the mRNA is highly expressed. H_1 receptors are also abundant in guinea pig thalamus, hypothalamic nuclei (e.g., ventromedial nuclei), nucleus accumbens, amygdaloid nuclei, and frontal cortex but not in neostriatum (20), whereas they are more abundant in the human neostriatum (29). The H_1 receptor was visualized in the primate and human brain *in vivo* by positron emission tomography using [^{11}C]mepyramine (30).

Blockade of H_1 receptors located in cerebral areas involved in wakefulness and cognition, and including those mediating excitation of thalamic relay neurons (31), neocortical pyramidal neurons (28) and ascending cholinergic neurons (32,33), presumably accounts for the sedative properties of "antihistamines" of the first generation.

Histamine H_2 Receptor

The molecular properties of the H_2 receptor remained largely unknown for a long time. Reversible labeling of the H_2 receptor was achieved using [^{3}H]tiotidine or, more reliably, [^{125}I]iodoaminopotentidine (2).

By screening cDNA or genomic libraries with homologous probes, the intronless gene encoding the H_2 receptor was first identified in dogs (34) and, subsequently, in other species including humans (1). The H_2 receptor is organized like other receptors positively coupled to adenylyl cyclase: it displays a short third intracellular loop and a long C-terminal cytoplasmic tail.

Using transfected cell lines, positive linkage of the H_2 receptor with adenylyl cyclase was confirmed, and unexpected inhibition of arachidonate release and stimulation of Ca^{2+} transients was evidenced (1). Hence H_2 receptor stimulation can trigger intracellular signals either opposite or similar to those evoked by H_1 receptor stimulation. Parallel observations were made for a variety of biological responses mediated by the two receptors in peripheral tissues.

Helmut Haas and colleagues showed that, in hippocampal pyramidal neurons, H_2-receptor stimulation potentiates excitatory signals by decreasing a Ca^{2+}-activated K^+ conductance, presumably by cAMP production (26). H_2-receptor activation depolarizes thalamic relay neurons slightly and increases apparent membrane conductance markedly, responses caused by enhancement of the hyperpolarization-activated cation current I_h (27). In addition to these short-lasting effects, histamine also induces very long-lasting increases in excitability in the CA1 region of the hippocampus through activation of H_2 receptors and the cAMP/cAMP-dependent protein kinase signal transduction cascade. This process is modulated by other receptors such as the H_1 receptor (35).

The sole selective H_2-receptor antagonist known to enter the brain is zolantidine, a compound used sometimes in animal behavioral studies but not introduced in therapeutics (36). However, some tricyclic antidepressants are known to block H_2-receptor–linked adenylyl cyclase potently and interact with [^{125}I]iodoaminopotentidine binding in a complex manner (37).

Autoradiographic localization of the H_2 receptor in guinea pig (20) and human brain (29) shows it distributed heterogeneously. The H_2 receptor is found in most areas of the cerebral cortex, with the highest density in the superficial layers, the piriform, and the occipital cortices, which contain low H_1-receptor density. The caudate putamen, the ventral striatal complex, and the amygdaloid nuclei (bed nucleus of the stria terminalis) are among the richest brain areas. In the hippocampal formation, the relative localizations of the H_2 receptor and its gene transcripts are similar to those observed for the H_1 receptor: the gene transcripts are expressed in all pyramidal cells of the Ammon horn and in granule cells of the dentate gyrus (38), whereas the H_2 receptor is expressed in the molecular layers of these areas, which contain the dendritic trees of the mRNA-containing neurons. The partial overlap with the H_1 receptor may account for their synergistic interaction in cAMP accumulation.

Histamine H_3 Receptor

The H_3 receptor was initially detected as an autoreceptor controlling histamine synthesis and release in brain. Thereafter, it was shown to inhibit presynaptically the release of other monoamines in brain and peripheral tissues as well as of neuropeptides from unmyelinated C fibers (39,40).

Reversible labeling of this receptor was first achieved using the highly selective agonist [^{3}H](R)α-methylhistamine (2), then [^{3}H]N$^{\alpha}$-methylhistamine, a less selective agonist, was also proposed (19), as well as, more recently, [^{125}I]iodophenpropit and [^{125}I]iodoproxyfan, two antagonists (41).

The regulation of agonist binding by guanylnucleotides (39), and the sensitivity of several H_3-receptor–mediated

responses to pertussis toxin (42,43), suggested that the H_3 receptor was G_i/G_o protein coupled, a suggestion confirmed by the cloning of the corresponding human (44) and rodent (45) cDNAs. The H_3 receptor gene contains two introns in its coding sequence and several splice variants H_{3L} and H_{3S} differing by a stretch of 30 amino acids in the third intracellular loop, were identified (45). The existence of these variants may partly account for the apparent H_3-receptor heterogeneity in binding or functional studies (46).

Significant differences in the pharmacology of the human and rodent H_3 receptor (47) could be assigned to differences in only two amino acid residues in the third TM (48). In various cell lines, stimulation of the H_3 receptor, like that of other G_i-protein–coupled receptors, inhibits adenylate cyclase (44) or phospholipase C (42) and activates phospholipase A_2 (48a).

On neurons, the H_3 receptor mediates presynaptic inhibitions of release of several neurotransmitters, including histamine itself (2,39), norepinephrine, serotonin, dopamine, glutamate, GABA, and tachykinins (40), presumably by inhibiting voltage-dependent calcium channels (39,43).

Several H_3-receptor antagonists, such as thioperamide and ciproxifan, potently enhance histamine release *in vitro* and *in vivo* (2,39,49).This response was originally attributed to blockade of the inhibitory effects of endogenous histamine and was therefore used in many studies, such as behavioral studies, to delineate the functions of histaminergic neurons. However, these drugs were shown to act, in fact, as inverse agonists, and the native H_3 receptor in brain display high constitutive activity including *in vivo* (48a).

Autoradiography of the H_3 receptor in rat (50,51) and monkey brain shows it highly concentrated in the neostriatum, the nucleus accumbens, the cingulate and infralimbic cortices, the bed nucleus of the stria terminalis, and the substantia nigra pars lateralis. In contrast, its density is relatively low in the hypothalamus (including the tuberomammillary nucleus), which contains the highest density of histaminergic axons (and perikarya), a finding indicating that most H_3 receptors are not autoreceptors. In agreement with this concept, intrastriatal kainate strongly decreases H_3 binding sites in the forebrain (as well as in the substantia nigra, consistent with their presence in striatonigral neurons) (50,51). In the human brain, the high densities of H_3 receptors found in the striatum and globus pallidus (29) were lower in patients with Huntington disease, a finding suggesting that the H_3 receptor is also located on striatonigral projection neurons of the direct and indirect pathways (52). Consistent with the proposal that most H_3 receptors are not autoreceptors, a strong expression of H_3-receptor mRNAs was observed not only within the tuberomammillary nucleus, but also in various regions of the rat (44) and guinea pig (45) brain, including the cerebral cortex, the basal ganglia, and the thalamus.

Interaction with NMDA Receptors

Histamine potentiates NMDA-evoked currents in acutely dissociated and cultured hippocampal and cortical neurons, an effect that could not be ascribed to activation of the known histamine receptors (17,18), but rather of a novel recognition site on NMDA receptors containing the subunits NR1A/NR2B (53).

Histamine may play a role in modulating the functions of NMDA receptors *in vivo*. It facilitates the NMDA-induced depolarization of projection neurons in cortical slices (54) and phase shifts the circadian clock by a direct potentiation of NMDA currents in the suprachiasmatic nucleus (55). Histamine, presumably acting through NMDA receptors, facilitates the induction of long-term potentiation and causes long-lasting increases of excitability in the CA1 region of rat hippocampal slices (35).

The histamine-induced modulation of NMDA responses is higher under slightly acidic conditions (56), which occur during hypoxia or epileptiform activity. This may lead to enhancement of neurotransmission or histamine-mediated neuronal death such as that observed in a rat model of Wernicke encephalopathy (57).

HISTAMINERGIC NEURON ACTIVITY AND THEIR CONTROL

Electrophysiologic Properties

Cortically projecting histaminergic neurons share with other aminergic neurons certain electrophysiologic properties evidenced by extracellular recording. They fire spontaneously slowly and regularly, and their action potentials are of long duration (26). Among the pacing events that may contribute to their spontaneous firing, tuberomammillary neurons exhibit a tetrodotoxin-sensitive persistent Na^+ current (58), a Ca^{2+} current probably of the low-threshold type (59), and multiple high-voltage–activated Ca^{2+} currents (43). In addition, they exhibit inward rectification attributed to an I_h current that may increase whole-cell conductance and may decrease the efficacy of synaptic inputs during periods of prolonged hyperpolarization , that is, when histaminergic neurons fall silent (60).

Modulation of Histamine Synthesis and Release *In Vitro*

The autoreceptor-regulated modulation of histamine synthesis in, and release from, brain neurons is well documented (2). It was initially evidenced in brain slices or synaptosomes after labeling the endogenous pool of histamine using the [^{3}H]histamine precursor. Exogenous histamine decreases the release and formation of [^{3}H]histamine induced by depolarization, and analysis of these responses led to the pharmacologic definition of H_3 receptors. The auto-

regulation was found in various brain regions known to contain histamine nerve endings, a finding suggesting that all terminals are endowed with H_3 autoreceptors.

Regulation of histamine synthesis was also observed in the posterior hypothalamus (39), and somatodendritic H_3 autoreceptors inhibit the firing of tuberomammillary neurons (26) by modulating high-voltage–activated calcium channels (43).

Galanin, a putative cotransmitter of a subpopulation of histaminergic neurons, regulates histamine release only in regions known to contain efferents of this subpopulation, that is, in hypothalamus and hippocampus but not in cerebral cortex or striatum (61). In brain slices, galanin also hyperpolarizes and decreases the firing rate of tuberomammillary neurons (26). It is not known, however, whether these galanin receptors behave as "autoreceptors" modulating galanin release from histaminergic nerve terminals, inasmuch as the tuberomammillary nucleus receives a strong galaninergic innervation from the ventrolateral preoptic area (12,13). Other putative cotransmitters of histaminergic neurons failed to affect [^{3}H]histamine release from slices of rat cerebral cortex (62). However, GABAergic inhibitory postsynaptic potentials are mediated by $GABA_A$ receptors located on histaminergic neurons (63). To what extent these receptors play an autoinhibitory role is unclear. A subpopulation of histaminergic neurons contains GABA (5), but the tuberomammillary nucleus also receives dense GABAergic innervation (12,13,15).

[^{3}H]Histamine synthesis and release are inhibited in various brain regions by stimulation of not only autoreceptors but also α_2-adrenergic receptors, M_1-muscarinic receptors, and κ-opioid receptors (2). Because these regulations are also observed with synaptosomes (62), all these receptors presumably represent true presynaptic heteroreceptors. In contrast, histamine release is enhanced by stimulation of nicotinic receptors in rat hypothalamus (64) and by μ-opioid receptors in mouse cerebral cortex (2).

Some molecular mechanisms regulating neuronal histamine dynamics remain unclear. *N*-methylation catalyzed by histamine *N*-methyltransferase is the major process responsible for termination of histamine actions in the brain (2), and genetic polymorphisms for the enzyme have been associated with altered levels of its activity (65). No histamine transporter could be evidenced, and direct feedback inhibition of histidine decarboxylase by histamine has been excluded (2).

Changes in Histaminergic Neuron Activity *In Vivo*

Both neurochemical and electrophysiologic studies indicate that the activity of histaminergic neurons is high during arousal. In rat hypothalamus, histamine levels are low, whereas synthesis is high during the dark period, a finding suggesting that neuronal activity is enhanced during the active phase (2). In mouse cerebral cortex, striatum, and hypothalamus, telemethylhistamine levels are doubled at the end of the dark phase of the cycle as compared with the beginning of the light phase (66). Histamine release from the anterior hypothalamus of freely moving rats, evaluated by *in vivo* microdialysis, gradually increases in the second half of the light period and is maintained at a maximal level during the active phase (67). Such state-related changes are also found in single-unit extracellular recordings performed in the ventrolateral posterior hypothalamus of freely moving cats. Neurons with properties consistent with those of histaminergic neurons exhibited a circadian rhythm of their firing rate, falling silent during deep slow-wave or paradoxical sleep (2). An important determinant of this circadian rhythm of tuberomammillary histaminergic neuron activity is a GABAergic inhibitory pathway originating in the ventrolateral preoptic area and activated during sleep (12,15).

A feeding-induced increase in the activity of histaminergic neurons has also been shown by microdialysis performed in the hypothalamus of conscious rats (68). Histaminergic neurons are a target for leptin in its control of feeding is unclear. An enhancement of histamine turnover was observed after intracerebroventricular infusion of leptin (70). Changes in the metabolism and release of histamine observed *in vivo* after occlusion of the middle cerebral artery in rats suggest that the histaminergic activity is also enhanced by cerebral ischemia (71).

Whereas H_1 and H_2 receptors are apparently not involved, inhibition mediated by the H_3-autoreceptor constitutes a major regulatory mechanism for histaminergic neuron activity under physiologic conditions. Administration of selective H_3 receptor agonists reduces histamine turnover (2) and release, as shown by microdialysis (72). In contrast, H_3-receptor antagonists enhance histamine turnover (2,49) and release *in vivo* (73,74), a finding suggesting that autoreceptors are tonically activated.

Agents inhibiting histamine release *in vitro* through stimulation of presynaptic α_2-adrenergic or muscarinic heteroreceptors reduce histamine release and turnover *in vivo,* but systemic administration of antagonists of these receptors does not enhance histamine turnover, a finding suggesting that these heteroreceptors are not tonically activated under basal conditions.

Activation of central nicotinic receptors inhibits histamine turnover (75). Several types of serotonergic receptors are likely to modulate histamine neuron activity. 5-Hydroxytryptamine $(5\text{-HT})_{1A}$–receptor agonists inhibit (76), whereas 5-HT_2–receptor antagonists enhance (77), histamine turnover in various brain regions. Stimulation of D2 (but not D3) dopamine receptors by endogenous dopamine released by amphetamine increases histamine neuron activity (77,78).

Histamine turnover in the brain is rapidly reduced after administration of various sedative drugs such as ethanol, Δ^9-tetrahydrocannabinol, barbiturates, and benzodiaze-

pines (2), presumably as a result of their interaction with GABA receptors present on nerve endings and on perikarya of histaminergic neurons (63,79).

In contrast, stimulation of μ-opioid receptors enhances histamine turnover in brain (2). NMDA receptors increase *in vivo* release of histamine from the anterior hypothalamus (80). Activation of NMDA and non-NMDA receptors in the diagonal band of Broca, the lateral preoptic area, and the anterior hypothalamic area led to inhibition or enhancement of firing rates of tuberomammillary neurons (15).

PHYSIOLOGIC ROLES OF HISTAMINERGIC NEURONS

In spite of many different suggestions mainly derived from the observations of responses to locally applied histamine, only a few physiologic roles of histaminergic neurons appear relatively well documented.

Arousal

Our initial proposal in 1977 (81) that histaminergic neurons play a critical role in arousal has been confirmed by data from a variety of experiments mainly performed by Lin and Jouvet in cats (33) and Monti in rats (2). In agreement with this concept, ablation of these neurons and inhibition of histamine synthesis, release, or action by the H_1 receptor decrease wakefulness and increase deep slow-wave sleep; conversely, inhibition of histamine methylation or facilitation of histamine release by H_3 receptor blockade increase arousal (49).

The arousing effect of histamine may result from H_1 and H_2-receptor–mediated depolarization of thalamic relay neurons that induces a shift of their activity from burst firing (predominating in deep sleep during which they are poorly responsive to sensory inputs) to single spike activity (predominating in arousal during which sensory information is more faithfully relayed) (31). Arousal may also result from H_1-receptor–mediated excitation of neocortical pyramidal neurons by the same mechanism as in thalamus, that is, reduction of a background leakage potassium current (28). Finally, arousal may occur indirectly by H_1-receptor–mediated excitation of ascending cholinergic neurons within the nucleus basilis or mesopontine tegmentum (32, 33), which also induces cortical activation.

All these cellular actions of histamine, together with observations that tuberomammillary neuron firing is maximal during wakefulness, suggest that histaminergic systems make an important contribution to the control of arousal. The circadian changes in histaminergic neuron activity seem to be directed by two major neuronal inputs arising from the anterior hypothalamus. The first ones are slow-wave sleep-activated inhibitory GABA- and galanin-containing neurons arising from the ventrolateral preoptic area (12,13); in contrast, neurons releasing the neuropeptide orexin that emanate from the lateral hypothalamus appear to exert opposite actions because disruption of the orexin gene is associated with narcolepsy in dogs and knockout mice (14,82). Other monoaminergic neurons participating in control of sleep and wakefulness states as well as GABA/galanin ventrolateral preoptic neurons also receive inputs from orexin neurons, which are, themselves, likely influenced by photic signals from the suprachiasmatic nucleus. In turn, neurons from the suprachiasmatic nucleus and the preoptic area seem to be influenced in a complex manner by histaminergic inputs (83,84). Hence a complex neuronal network in the hypothalamus with reciprocal influences involving histaminergic neurons seems to control wakefulness.

The major part played by the H_1 receptor in these processes, confirmed in mutant mice lacking this receptor (85), accounts for the sedating effects of the first generation of "antihistamines," that is, antagonists that easily enter the brain and are still ingredients of over-the-counter sleeping pills (86). It may also account for the sedative side effects of many antipsychotic or antidepressant drugs that are potent H_1 antagonists.

Cognitive Functions

The idea that histaminergic neurons may improve cognitive performance is consistent with projections of these neurons to brain areas such as the prefrontal and cingulate cortices or hippocampus, their excitatory influences therein, and their positive role in wakefulness.

Ciproxifan, a potent and selective H_3-receptor antagonist (or inverse agonist), which strongly enhances histamine turnover in brain, improved attentional performances in the rat five-choice test under conditions similar to those of drugs enhancing cholinergic transmissions (49). Various H_3 antagonists facilitate various forms of learning. They improve short-term social memory in rats (87), reverse the scopolamine- or senescence-induced learning deficit in a passive avoidance test in mice (88), and facilitate retention in a footshock avoidance test in mice (89).

Generally, H_3 agonists exert opposite effects, and the effects of H_3-antagonists are reversed by H_1 antagonists, a finding that suggests that these effects are attributable to enhanced histamine release. In contrast to the large body of experiments indicating a "procognitive" role of tuberomammillary neurons, Huston and coworkers repeatedly showed that excitotoxic lesions aimed at these neurons ablation result in improvement of learning in a variety of tests (e.g., ref. 90). The discrepancy with data from pharmacologic approaches may result from the difficulty to achieve selective histamine neuron ablation.

Control of Pituitary Hormone Secretion

Histamine affects secretion of several pituitary hormones (2,91). Magnocellular neurons of the supraoptic and para-

ventrical nuclei are typically excited, an essentially H_1-receptor–mediated response resulting in enhanced blood levels of vasopressin and oxytocin. Histaminergic neurons are activated during dehydration, parturition, and lactation, and histamine release onto magnocellular neurons participates in the control of these physiologic processes by the neurohypophysial hormones (92,93).

Histaminergic neurons may also participate in the hormonal responses to stress. In agreement with this concept, they are activated during various forms of stress and heavily project to hypothalamic or limbic brain areas (e.g., the amygdala or bed nucleus of the stria terminalis) involved in these responses. Various pharmacologic studies have shown the participation of endogenous histamine by H_1- and H_2-receptor stimulation in the adrenocorticotropic hormone–corticosterone, prolactin, or renin responses to stressful stimuli such as restraint, endotoxin, or dehydration (94). Many histaminergic neurons contain estrogen receptors, project to luteinizing hormone–releasing hormone neurons in preoptic and infundibular regions, and may constitute, by H_1-receptor stimulation, an important relay in the estradiol-induced preovulatory luteinizing hormone surge (95).

Satiation

Weight gain is often experienced by patients receiving H_1 antihistamines as well as by patients taking antipsychotics or antidepressants displaying potent H_1-receptor antagonist properties. These effects reflect the inhibitory role of endogenous histamine on food intake mediated by the H_1 receptor, namely, on the ventromedial nucleus (97). Histamine neurons projecting to the hypothalamus may be responsible for the food intake suppression induced by leptin (70).

Seizures

The anticonvulsant properties of endogenous histamine were initially suggested from the occurrence of seizures in patients with epilepsy, particularly children, after administration of high doses of H_1-receptor antagonists crossing the blood–brain barrier, even those agents devoid of anticholinergic activity (86). These drugs, by completely occupying the H_1 receptor, as assessed by positron emission tomography studies (30), could block the histamine-induced reduction of a background-leakage K^+ current.

Drug-induced changes in histamine synthesis, release or metabolism confirmed the role of the endogenous amine acting through the H_1 receptor in preventing seizure activity elicited by pentetrazol, transcranial electrical stimulation, or amygdaloid kindling . Acquired amygdaloid kindling susceptibility appears associated with reduced histamine synthesis in limbic brain areas (97). In addition, kainic acid–induced limbic seizures are accompanied by up-regulation of the H_1-receptor mRNA in striatum and dentate gyrus, a finding consistent with a regulatory role of this receptor in seizure activity (98).

Nociception

The antinociceptive effects of histidine loads, H_3-receptor antagonists, and histamine *N*-methyltransferase inhibitors, as well as opposite effects of histamine synthesis inhibitors or H_3 agonists, support the idea that brain histamine inhibits nociceptive responses such as the mouse hot plate jump (99). In contrast, peripherally acting H_3-receptor agonists prevent nociceptive responses such as mouse abdominal constriction by inhibiting sensory C-fiber activity (100).

ROLE OF HISTAMINERGIC NEURONS IN NEUROPSYCHIATRIC DISEASES

Among the various approaches that tend to establish the implication of other neuronal systems in neuropsychiatric diseases, so far only a few have been applied to histamine.

Histamine, Schizophrenia, and Antipsychotic Drug Actions

Overdose of various classic H_1 antagonists was repeatedly reported to result in toxic psychoses with hallucinations resembling schizophrenia, and the hallucinogenic potential of these drugs has even led to abuse (86). Conversely, metamphetamine, a drug with hallucinogenic potential and to which patients with schizophrenia seem hyperresponsive, releases histamine in rodent brain areas, an indirect effect mediated by stimulation of D2 and not D3 dopamine receptors (77,78). Even more, endogenous dopamine appears to exert a tonic stimulation of histamine neurons because typical neuroleptics, such as haloperidol, decrease their activity. In contrast, atypical neuroleptics, such as clozapine, enhance histamine turnover, an effect related to 5-HT_2 receptor blockade and possibly underlying their procognitive properties (77). The locomotor activation elicited in rodents by amphetamine and other dopaminergic agonists is attenuated by H_3-receptor blockade (101). Repeated amphetamine administration to rodents that results in behavioral sensitization to dopamine agonists, a cardinal feature of schizophrenia, is accompanied by enhanced histamine release, a finding that presumably reflects an enhanced tonic dopaminergic influence on histaminergic neurons (77,78). In one comprehensive study, an enhanced level of *t*-methylhistamine, the major histamine metabolite, was detected in the cerebrospinal fluid of patients with schizophrenia, who were either treated or untreated with neuroleptic agents (102).

In several open studies, famotidine, an H_2 antagonist, was found to improve schizophrenia in patients, a finding

that remains to be confirmed in control studies. A previous claim of association between polymorphisms of the H_2-receptor gene and schizophrenia could not be confirmed (103).

These various observations, although not readily forming a coherent picture, suggest that histaminergic neuron activity is enhanced in patients with schizophrenia, and blockade of H_2 or H_3 receptors could be useful in the treatment of this disease.

Histamine and Alzheimer's Disease

Neuropathologic studies have documented a deficit in histaminergic neurotransmission in Alzheimer's disease. In some, but not all, cortical areas (e.g., the frontal or temporal cortex) of brains affected by Alzheimer's disease, there is a decrease of histamine and histidine decarboxylase levels that may reach up to approximately 50% (104), and the expression of the *hdc* gene in neurons of the tuberomammillary nucleus is also reduced (S. Trottier, personal communication). Decreased histaminergic input may affect cholinergic neuron activity in the nucleus basilis (32) and acetylcholine release in cortical areas.

If one takes into account an additional direct positive influence of histamine on attention and memory, this indicates that enhancing histaminergic neurotransmission may constitute a novel symptomatic therapeutic approach to Alzheimer's disease. The drug tacrine was even more potent in inhibiting histamine-*N*-methyltransferase, the main histamine-metabolizing enzyme, than acetylcholinesterase (105).

Histamine and Other Neuropsychiatric Disorders

Anxiety may be increased by endogenous histamine acting at the H_1 receptor. In agreement with this concept, H_1-receptor knockout mice display significantly less anxiety in the elevated maze test (106). However, the utility of H_1-receptor antagonists in anxiety disorders is not established.

Patients with *attention-deficit disorders* may benefit from enhanced histamine release, as suggested by the therapeutic effect of amphetamine in children and the attention-enhancing effects of an H_3-receptor antagonist in the rat (49).

Antidepressant-like effects in the mouse forced swim test result from enhanced histamine release and H_1-receptor activation (107).

CONCLUSION

This chapter describes how our knowledge of the molecular neurobiology of cerebral histaminergic systems and their implications in physiologic functions, such as arousal or hormonal regulations, have progressed over the years. In contrast, little is known, so far, about their possible implications in neuropsychiatric diseases and the therapeutic utility of psychotropic drugs to affect their activity. H_3-receptor antagonists (or inverse agonists) that markedly enhance brain histamine release are currently undergoing clinical trials. It seems likely that the next edition of this book will see their place in therapeutics established.

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