

Histamine in the Nervous System

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I. INTRODUCTION

This physiological review covers the histaminergic system in the mammalian brain from molecule to mind with brief descriptions of invertebrate and peripheral mammalian systems. In consideration of several recent authoritative reviews, the pharmacology of histamine receptors is not treated extensively. Information in this review is largely derived from peer-reviewed literature and references indexed in the PubMed database of the National Library of Medicine. A comprehensive search on “histamine” through 2008 in PubMed using a complex search strategy including wildcards and medical subheadings (MeSH) covering terms such as antihistamines and tuberomammillary nucleus, reveals more than 92,000 references, a result comparable to that found for other biogenic amines. Only ~2,500 (500 reviews, 100 clinical trials) of these references deal with histamine in the nervous system, and <0.4% (~340) focus on the histaminergic tuberomammillary nucleus in the hypothalamus. Thus there is a mismatch between the number of publications on and the biological significance of the brain histamine system. The time has come for the integration of novel information, in the light of increasing interest in the physiology and pathophysiology of this evolutionary conserved aminergic system that enables the organism to cope with environmental challenges and novelty.

II. HISTORY

The name histamine for imidazolethylamine indicates an amine occurring in tissues. The presence and biological activities of histamine were detected by Sir Henry Dale and co-workers almost a century ago: con-

traction of smooth muscles in the gut and vasodilatation (130). The stimulation of acid secretion in the stomach (582) was also recognized early. Feldberg (172) demonstrated histamine release from mast cells in the lungs during anaphylactic shock causing constriction of the bronchi. The presence of histamine in the brain, predominantly in the gray matter, was first shown by Kwiatkowski (1941) (378), and White (1959) (814) demonstrated its formation and catabolism in the brain. The sedative “side effects” of antihistamines (68) triggered early work and suggestions for histamine as a “waking substance” (488). Advances in biochemical methodology revealed more details about the synthesis by the dedicated enzyme histidine-decarboxylase and the rapid turnover of histamine in the brain (578, 652, 744, 745).

In the 1960s, the other biogenic amines became visible, fluorescent through *o*-phthalaldehyde histochemistry (96), and the exact localization of the catecholaminergic and serotonergic systems with their involvement in major neuropsychiatric diseases attracted an overwhelming interest of neuroscientists. At this time, brain histamine became neglected in spite of the indirect demonstration of histaminergic neurons and their functional projections (193). The reason for the failure of phthalaldehyde fluorescence histochemistry for histamine was a strong cross-reaction with the ubiquitous spermidine (common actions of the diamine histamine and the polyamine spermidine on the NMDA receptor were found 25 years later). Effects of histamine and histamine antagonists on single nerve cells in several regions of the central nervous system (CNS) as well as distinct influences on behavior after infusion in cerebral ventricles or brain regions were highly suggestive for a transmitter action, but this role gained recognition very slowly. Jack Peter Green at

Mt.Sinai in New York was a major advocate for histamine in the brain (218).

The definition of histamine H₂R by Sir James Black and his group revolutionized the treatment of stomach ulcers (59), but in spite of the presence of H₂R and important cellular actions in the brain, the breakthrough had to await the histochemical documentation of histaminergic neurons by the group of Hiroshi Wada in Osaka and Pertti Panula in Washington: seeing is believing. The tuberomammillary nucleus in the posterior hypothalamus contains the histaminergic neurons with projections all over the CNS just like the other amine systems (551, 803, 804) (Fig. 1). All amine systems feature autoreceptors providing a negative feedback on excitability, release, and synthesis. Jean-Charles Schwartz, who played a central role in the histamine case, with his group in Paris identified the H₃ autoreceptors that control the activity of histaminergic neurons: histamine synthesis, release, and electrophysiology (32). For more details on the history of histamine research, see Reference 557.

III. NONNEURONAL HISTAMINE

Histamine occurs in cells of neuroepithelial and hematopoietic origin and serves distinct functions: gastric acid secretion, immunomodulation, smooth muscle contraction (bronchial), vasodilatation (vascular), as well as epi- and endothelial barrier control. These actions have important implications for gastrointestinal, immune, cardiovascular, and reproductive functions.

A. Gastrointestinal System

The vagus nerve regulates histamine mobilization from enterochromaffin-like cells of the stomach (241, 242)

by controlling their sensitivity to gastrin (523), and histamine controls gastric acid secretion by activating the proton pump in parietal cells through H₂R activation (598). H₂R antagonists are used for treating peptic ulcer disease. Studies in histamine-deficient animals (HDC-KO mice) unequivocally confirmed that *de novo* histamine synthesis is essential for gastric acid secretion induced by gastrin, but not vagally released acetylcholine, which cooperates in acid production (736). Histamine released from mast cells, closely associated with immune responses against gut microbiota, plays a role in gastrointestinal tract infection, inflammation, and tumor genesis. A sparse network of histamine immunoreactive fibers seems to derive from the submucous ganglion cell layer (545). All histamine receptors, H₁R-H₄R, have excitatory actions on enteric neurons and are found in the whole intestine and enteric nervous system in humans (73). Elevated levels of H₁R and H₂R are found in endoscopic biopsies from humans with food allergy and irritable bowel syndrome (633).

B. Immune System

Histamine plays a central role in innate and acquired immunity: in allergy and inflammation, closely associated with mast cell functions (157, 467), in immunomodulation regulating T-cell function (318) and autoimmunity (435, 500, 564, 748, 749). Histamine synthesis, signaling, and function is controlled by a variety of immune signals and, in turn, modulates cytokine and interferon networks and function. Histamine-deficient animals (HDC-KO mice) show elevated levels of proinflammatory cytokines [interferon (IFN)- γ , tumor necrosis factor (TNF)- α , and leptin] (500, 564). The gene encoding the H₁R is an important autoimmune disease locus (435) identical to that of *Bor*-

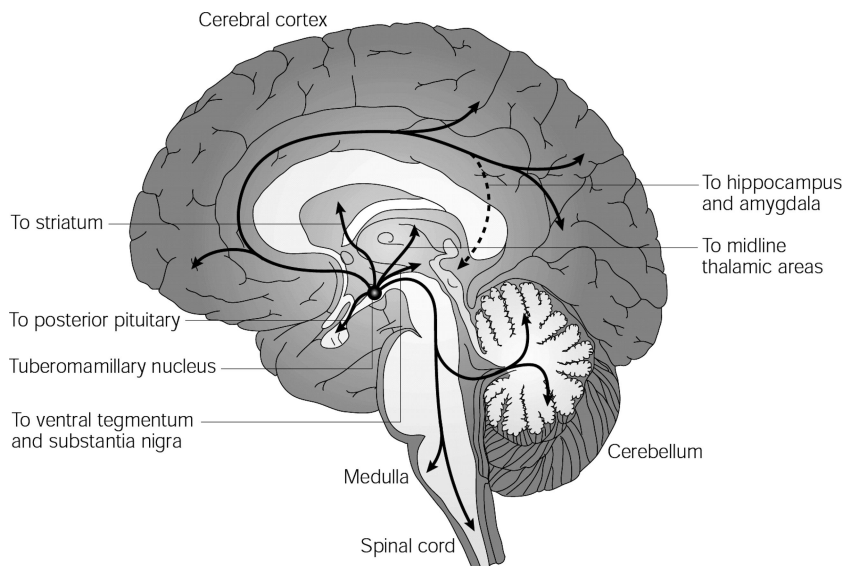


FIG. 1. The histaminergic system in the human brain. The histaminergic fibers emanating from the tuberomammillary nucleus project to and arborize in the whole central nervous system. [Modified from Haas and Panula (235).]

detella pertussis toxin sensitization (Bphs), which controls both histamine-mediated autoimmune T cell and vascular responses after pertussis toxin sensitization. Histamine H1R- and H2R-deficient mice have an imbalance in Th1/Th2 cell function (318, 564) and a lower susceptibility to develop autoimmunity (435, 748, 749). In contrast, more severe autoimmune diseases and neuroinflammation are observed in mice lacking H3R (749), the receptor confined to the CNS and controlling brain histamine levels. H4R on immune cells regulate cell migration and allergic responses in the periphery (135), and together with neuronal H3R may control trigeminovascular function, blood-brain barrier permeability, and immigration of immune cells into the otherwise immunoprivileged CNS (749). The elaborate interactions of histamine in the immune and nervous system (704, 713, 751) are certainly relevant for the diseased brain, but also for physiological adaptive and plastic processes subserving homeostatic and integrative higher brain functions.

Mast cells play a fundamental role in immunity and allergic responses in the periphery (157, 467) as well as in the CNS, where they may act as gatekeepers at interfaces between the nervous and immune systems (704, 713, 751). In peripheral connective tissues, near blood vessels and in the enteric mucosa, they store and release histamine and other signaling molecules in response to antigen exposure and other pathological conditions associated with tissue injury, inflammation, and autoimmunity. Compound 48/80, a basic polymer, causes exocytosis of mast cell granular content but not of histamine from axonal varicosities (157, 467) and thus can differentiate histamine release from nonneuronal and neuronal resources. The expression of HDC in brain microvasculature is controversial (329, 830).

Mast cells in circumventricular organs, in the meninges, hypophysis, pineal gland, area postrema, the median eminence, hypothalamus, and along blood vessels in the gray matter contain a significant component of brain histamine, a pool that turns over much more slowly than neuronal histamine (144, 268, 577). Mast cells can rapidly enter the brain, particularly under pathological conditions (751). Their number also varies greatly between species, regions, time of the year and of the day, age, sex, and behavioral state (682, 683). During a transitional phase in development (P11–13), mast cells migrate along blood vessels of the fimbria and hippocampus and penetrate into the thalamus (382), where they reside in adulthood (178, 210). This suggests a high affinity of mast cells to structures in the developing brain and regions exhibiting a high degree of adaptive rewiring and structural rearrangement throughout life. A striking example for this with behavioral implication is the massive immigration of gonadotropin releasing hormone (GnRH)-containing mast cells in the dove habenula during courtship (682). Histamine from mast cells in the median eminence may well

affect hypothalamic neurons involved in endocrine control and homeostatic regulation (333, 455).

IV. METABOLISM (SYNTHESIS, TRANSPORT, INACTIVATION)

Histamine (CID 774) is synthesized from the amino acid histidine through oxidative decarboxylation by histidine-decarboxylase (HDC; EC 4.1.1.22), a pyridoxal 5'-phosphate (PLP)-dependent enzyme (177) found in many species and highly conserved throughout the animal kingdom from mollusc, insect, rodent, to human (19, 177, 498, 606, 625). Restricted and cell-specific expression of HDC in peripheral tissues is controlled at both transcriptional (DNA methylation) (376, 717) and posttranslational levels [ubiquitin-proteasome (177, 532), caspases (189)]. Little is known about specific regulation of HDC gene expression in the brain. However, neuroactive peptides, such as gastrin and pituitary adenylate cyclase-activating polypeptide (PACAP) (464), steroids, such as glucocorticoids (329, 849), and other factors control HDC gene promoter activity and also protein degradation in various tissues and contexts (e.g., oxidative stress) (6, 177, 258, 502, 598, 852). The rate of histamine synthesis, in contrast to that of other biogenic amines, is determined by the bioavailability of the precursor; histidine is taken up into the cerebrospinal fluid and neurons through L-amino acid transporters (Fig. 2). HDC activity can be inhibited by α -fluoromethylhistidine (α -FMH), a suicide substrate leading to a marked depression of histamine levels (363). α -FMH has proven a useful tool to study histaminergic functions (194, 437, 438) but is difficult to synthesize and not commercially available at present.

Neuronal histamine is stored in cell somata and especially in axon varicosities (141, 252, 372, 451, 824), where it is carried into vesicles by exchange of two protons through the vesicular monoamine transporter VMAT-2 and released upon arrival of action potentials (158, 466, 806). The level of histamine in brain tissue is somewhat lower than that of other biogenic amines, but its turnover is considerably faster (in the order of minutes) and varies with functional state (144, 578). Brain histamine levels measured with implanted microdialysis tubes exhibit a marked circadian rhythmicity (see sect. IX) in accordance with the firing of histamine neurons during waking (483). Extracellular histamine levels in the preoptic/anterior hypothalamus follow the oscillations of different sleep stages [wakefulness > non-rapid eye movement (REM) sleep > REM sleep], but invariant histamine levels during sleep deprivation suggest that histamine may relay circadian rather than homeostatic sleep drive (584, 710). Philippu and Prast (569, 570) have demonstrated a direct correlation between histamine levels in the hypothalamus and behavioral state by electroencephalography. Synthe-

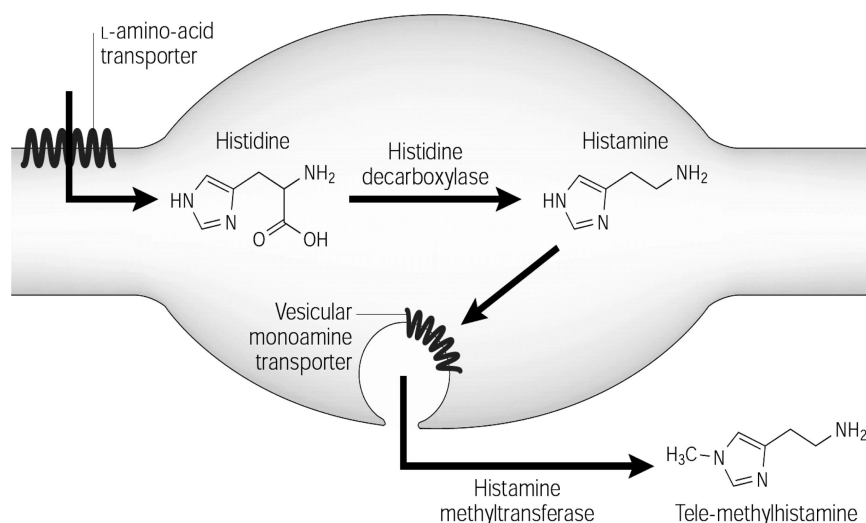


FIG. 2. Histamine synthesis and metabolism. Histidine is taken up in a varicosity and decarboxylated; histamine is transported into a vesicle, released, and methylated. [Modified from Haas and Panula (235).]

sis and release of histamine are controlled by feedback through H3 autoreceptors located on somata and axonal varicosities (31, 32, 589). Furthermore, the release of histamine is affected by transmitters impacting histamine neuron firing and/or release from varicosities bearing inhibitory m1-muscarinic, α 2-adrenergic, and peptidergic receptors (33, 227–229, 290–292, 570, 588).

Inactivation of histamine in the extracellular space of the CNS is achieved by methylation through neuronal histamine *N*-methyltransferase (HNMT; EC 2.1.1.8) (49, 69, 456) (Fig. 2). Histamine methylation requires *S*-adenosyl-methionine as the methyl donor (220, 592, 651). Blockers of HNMT reduce tele-methylhistamine and increase histamine levels in the brain (150). Histamine hardly passes the blood-brain barrier (751), but HNMT is also found in the walls of blood vessel where blood-borne histamine and histamine released from mast cells is methylated and inactivated (520). Moreover, a vectorial transport system (shuttle) from the brain to the vasculature may help to drain neuronal histamine after excessive surges. Tele-methylhistamine in the brain undergoes oxidative deamination through a monoamine oxidase (MAO-B) to *t*-methyl-imidazoleacetic acid (408, 595, 651). The main histamine-degrading enzyme in peripheral tissues (gut, connective tissues) and in invertebrates is diamine oxidase (DAO), which directly converts histamine into imidazoleacetic acid. DAO activity in the brain is negligibly low under basal conditions, but when HNMT is inhibited may represent a salvage pathway for production of imidazoleacetic acid, an effective GABA_A receptor agonist (266, 596).

V. INVERTEBRATES

Histaminergic neurons are found in mussels, snails, and squid. In *Aplysia*, the C2 cell, a complex mechanosen-

sor involved in feeding-related arousal, has long been known to be histaminergic (38, 156, 459, 653, 808). Histamine immunohistochemistry has identified cell clusters triggering the respiratory pumping as well as many further neurons in all central ganglia (150). Histamine induces excitatory and inhibitory synaptic potentials (216, 459) and modulations (109, 811) in a variety of follower cells (98).

Histamine-containing somata and fibers are widespread in arthropod brains, with the most intense labeling in the retinal photoreceptors and in the first optic ganglion, where the short visual fibers contact the monopolar neurons (507, 576, 711). Histamine is released from arthropod photoreceptors and gates chloride channels on postsynaptic interneurons; it mediates the light response of the postsynaptic large monopolar cells. Gengs et al. (202) have provided unequivocal evidence that histamine is the transmitter at the photoreceptor synapse of *Drosophila* and likely in all arthropods (247, 711, 854). In the compound eye of flies, output from photoreceptors that share the same visual field is pooled and transmitted via histaminergic synapses to two classes of interneurons, large monopolar and amacrine cells. Furthermore, histamine modulates insect clock neurons (244) and is crucial for insect temperature preferences (261). The *Drosophila* genes *tan* and *ebony* encode enzymes that hydrolyze and conjugate biogenic amines and represent a novel glia-based histamine trap and inactivation mechanism (64). Notably, *ebony* plays a central role in controlling *Drosophila* circadian locomotor rhythms (712). *Tan* is required for histaminergic neurotransmission in *Drosophila* and may be central to the understanding of pigmentation and photoreceptor function in general (767). Interestingly, histaminergic fibers innervate amacrine cells in the vertebrate retina, but there are no histaminergic cells in this structure (199). By systematic expression screening,

Gisselmann et al. (207) identified two cDNAs from *Drosophila* coding for histamine-gated chloride channels by functional expression in *Xenopus laevis* oocytes (207). Homomultimeric chloride channels are gated by histamine and GABA, blocked in the absence of an agonist by curare, all three types of histamine receptor antagonists, and picrotoxin but not bicuculline (206). The lobster CNS also contains histaminergic neurons, and a similar histamine-gated chloride channel mediates inhibition of odor-evoked spiking in olfactory receptor neurons (460).

VI. THE TUBEROMAMILLARY NUCLEUS

A. Development

The histaminergic system is well preserved through phylogeny from mollusc to human with a rather comparable morphological and functional disposition: a modulating system that activates the nervous systems according to environmental and metabolic challenges ranging from feeding-related arousal in the snail to novelty-associated waking and attention in vertebrates. The developmental pattern of histamine-immunoreactivity and HDC expression in the vertebrate embryonic body (and later in stem and cancer cells) indicates a largely unexplored general role of histamine in tissue homeostasis and plasticity (173, 253, 518, 547, 579).

A transient histaminergic system in rat brain is found around 2 wk after gestation (E13) at the border between mesencephalon and metencephalon, 2 days later in the ventral mesencephalon and rhombencephalon (36, 339, 605). This matches the location of adult serotonergic neurons. One week later (E20), the transient histaminergic system disappears and the first histamine-immunoreactive neurons shine up in the caudal tuberal diencephalon to form the tuberomamillary nucleus. By outgrowth and further maturation, the hypothalamic histamine system reaches an adultlike appearance 2 wk postnatally (P14). The functional significance of the transient histamine system is unknown but may support network plasticity during development. Interestingly, in the most primitive vertebrate, the lamprey, the transient system is preserved in adulthood. In all other adult vertebrates studied (fish, turtle, frogs, rodents, primates), the location of histaminergic neurons is restricted to the posterior hypothalamus. Eriksson (162) detected no other than the brain histamine system in the whole zebrafish, whose development can be followed *in vivo*. This opens intriguing opportunities to conduct a pharmacological analysis of endogenous histaminergic function *in vivo* simply by adding drugs to the aquarium water (565, 566, 608).

H3R blockade has, similar to methamphetamine exposure during early postnatal development, detrimental effects on higher brain functions in adulthood (3, 4, 327,

601). Therefore, careful evaluation of drugs that directly or indirectly affect histamine receptor-mediated signaling during development is warranted. Brain histamine and metabolite levels (595), but not HDC expression, increase while receptor densities decline with aging and may contribute to brain pathology and dysfunction in the elderly (254, 623, 747, 836, 837).

B. Anatomy

The reason for the relative neglect of the histaminergic system was its late precise morphological characterization. Early studies using lesions as well as biochemical and electrophysiological methods had revealed convincing evidence for the existence and the approximate location of the histaminergic neurons in the posterior hypothalamic region (143, 193, 230, 238), but only the exact morphological characterization by immunohistochemistry in the tuberomamillary nucleus (TMN) using antibodies against histamine and HDC (161, 361, 551, 701, 803, 804, 816, 824) initiated the slow process of general acceptance of the histaminergic system in the brain (Fig. 1). Tuberomamillary is the correct spelling derived from mamilla (not from mamma), although the term *tuberomamillary* is often indexed in scientific databases.

The histaminergic nucleus is located between the mamillary bodies and the chiasma opticum at the tuber cinereum (Fig. 2). For the rat, Ericson (161) subdivided the nucleus in a ventral group around the mamillary bodies close to the surface of the brain (TMV, ~1,500 neurons on each side), a medial group around the mamillary recess (TMM, ~600 neurons on each side), and a diffuse part (~200 scattered neurons) (161). Inagaki and co-workers (281, 799) describe five parts by further subdivision of the TMV in a rostral and caudal and the TMM in a dorsal and ventral part (E1–E5). The subdivisions are bridged by scattered neurons in keeping with the concept of one continuous cell group that got dispersed during development (804). Tracing studies have so far revealed only a low level of topographical organization; for instance, projections to the brain stem arise from more caudal parts of the TMN (349). There is evidence for heterogeneity within the histaminergic neuron population; this includes differential responses to environmental stimuli and stress (475), cannabinoids (100), GABA, and glycine, the latter according to specific subunit composition and stoichiometry of GABA_A receptors and neuron size, respectively (669).

The TMN in the mouse brain is less compact and contains fewer and smaller neurons than in the rat (556). The histaminergic neurons in the guinea pig are more widely distributed than in the rat and the mouse, extending in the supramamillary nucleus (10, 690). In the tree shrew (8) and in the cat (408, 410), the nucleus is rather

more compact and located mainly in the ventrolateral part of the posterior hypothalamus.

1. Human brain

The human histaminergic system is quite extensive with ~64,000 neurons in and around the tuberomammillary nucleus (Fig. 3). About the same number of noradrenergic neurons are found in the locus coeruleus. A detailed analysis of histaminergic projections in the human brain is not available, but a well-organized network of immunoreactive varicose fibers is seen, for instance, in the cortex with an emphasis on lamina I, where the fibers extend parallel to the pial surface (543). In the hypothalamus of rodents, the dendrites of TMN neurons make close contact to the brain surface, whereas in the human posterior hypothalamus, varicose axons accumulate in this location. In partial similarity to the rat, four subgroups of the histaminergic nucleus can be discerned: a major ventral part corresponding to the classical tuberomammillary nucleus, a medial part that includes also the supramammillary nucleus, a caudal paramammillary, and a minor lateral area. Thus the histaminergic neurons occupy a comparatively larger part of the posterior hypothalamus (9).

C. Cellular Morphology

The morphological characteristics of histaminergic neuron somata are similar throughout the species and to the aminergic neurons of the mesencephalon. They mostly possess large somata, 20–30 μm diameter (551, 804), with two or three large further subdividing dendrites

(824) that overlap with the dendrites of other histaminergic neurons (Fig. 4). Paired recordings have not revealed overt synaptic or electric (field) interactions between these neurons (Haas, unpublished data). Many dendrites approach the inner or outer surface of the brain and could make contact to the cerebrospinal fluid in the third ventricle (TMM) and the subarachnoidal space (TMV) (161). The axons arise mostly not from the soma but at some distance from a thick dendrite (161). In electron microscopic pictures, the histaminergic neurons display a large cytoplasm with a well-developed Golgi apparatus and many mitochondria. The large spherical nucleus contains a dark prominent nucleolus (141, 824) (Fig. 5).

The TMN of the rat (not the mouse) displays an intense immunohistochemical reaction towards adenosine deaminase (695). The number of stained cells is ~4,500 on each side, indicating that the population is not entirely congruent with the histaminergic neurons. A smaller cell type (~15 μm diameter) with less intense staining may be the nonhistaminergic group as HDC mRNA was never found in single neurons of this size (669). The varicose axons form a dense network in the hypothalamus. The function of adenosine deaminase located in the cytosol or the outer membrane of these neurons is unknown.

D. Cotransmitters

The TMN is the only source of neuronal histamine in the adult vertebrate brain, and histamine is its main transmitter. Nevertheless, further transmitters or their synthetic enzymes are expressed within TMN neurons (160, 373): GAD 65/67 indicate a GABAergic phenotype, but so

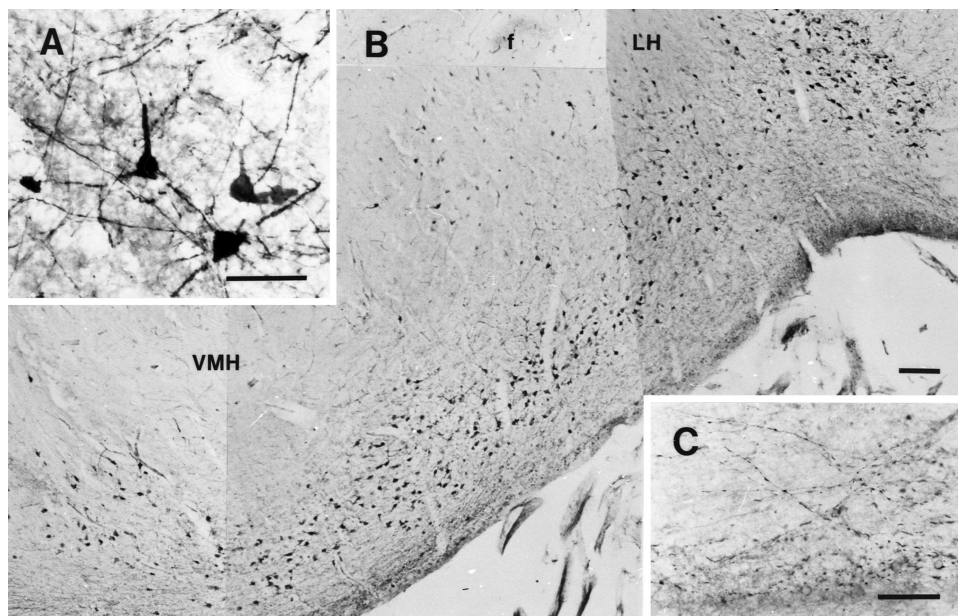


FIG. 3. Human hypothalamic histamine-immunoreactive neurons. A: large histaminergic neurons in the human tuberomammillary nucleus. B: histaminergic neurons in the human basal hypothalamus occupy a large area. The midline is on the left. C: a plexus of crossing fibers in the basal hypothalamus. Scale bar, 100 μm . [From Watanabe and Wada (Editors). *Histaminergic Neurons: Morphology and Function*. Boca Raton, FL: CRC, 1991. By permission from P. Panula, Helsinki.]

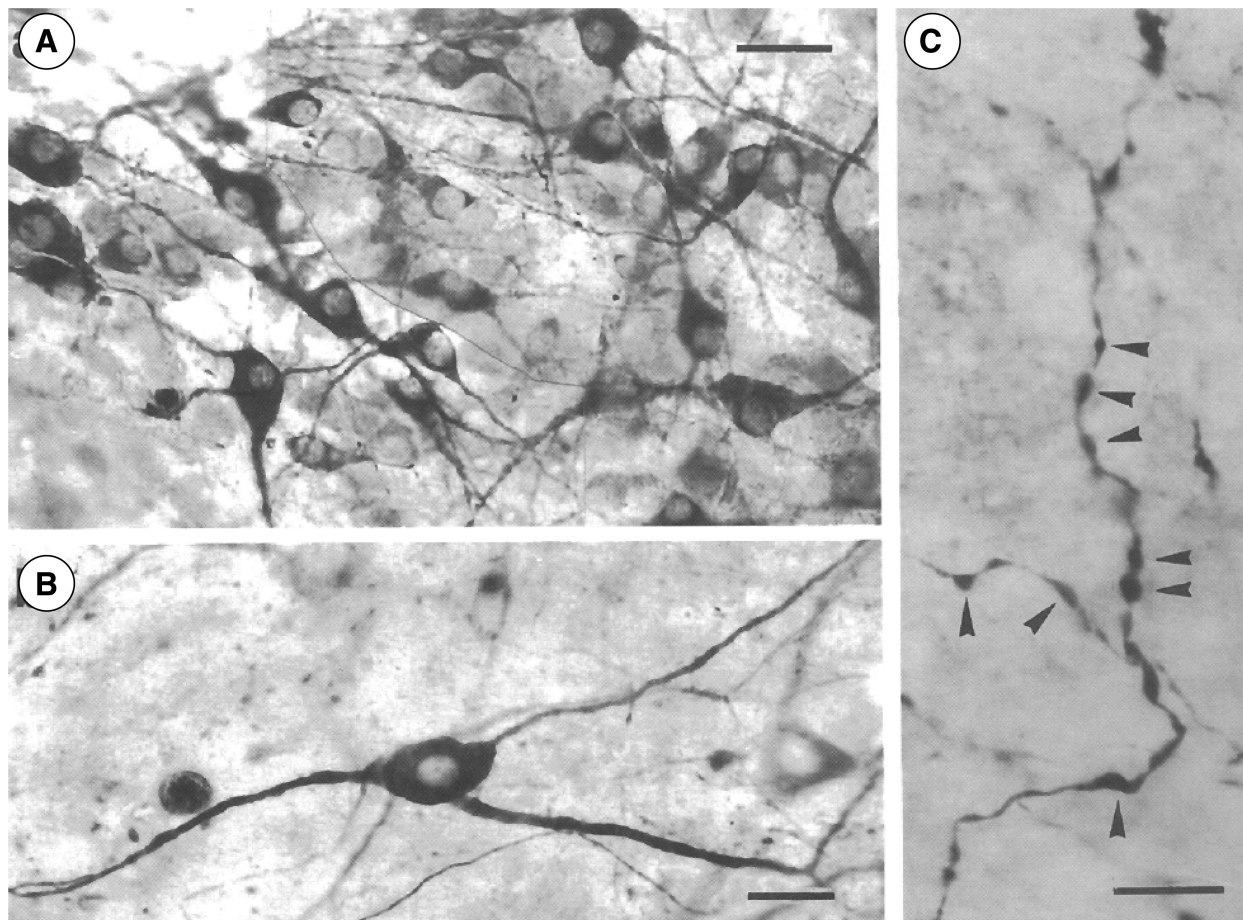


FIG. 4. Histaminergic (HDC-positive) neurons in an organotypic culture. *A*: from the dorsomedial part of the tuberomammillary nucleus. *B*: a single TMN neuron, 5 wk in culture. *C*: HDC immunoreactive fibers in the pyramidal layer of the cocultured hippocampus. Scale bars: *A*, 50 μm ; *B*, 25 μm ; *C*, 10 μm . [Modified from Diewald et al. (141).]

far, no evidence for effective release of GABA from TMN neurons is available. Should GABA be released from TMN axonal varicosities, the physiological impact would be expected to be significant and possibly opposite to the normal histamine release. The first paper describing the GABAergic nature of TMN neurons appeared before their identification as the histaminergic neurons (789). Subpopulations of TMN neurons express also galanin, enkephalins, thyrotropin releasing hormone (TRH), and substance P with some variation between species.

E. Electrophysiological Properties

Morphological and electrophysiological properties of histaminergic neurons are similar to those seen in other aminergic neuron populations (217). They display a slow regular firing pattern at 1–4 Hz in the absence of synaptic activation (236, 604) even in isolated neurons (779) (Fig. 6A). In behaving animals (cats, rats, mice), the firing pattern is more variable during waking and missing during

sleep (305, 407, 556, 724; for review, see Ref. 406). Recordings from immunohistochemically identified TMN neurons revealed a membrane potential of about -50 mV and a broad action potential (up to 2 ms mid-amplitude duration at 35°C) with a significant contribution from Ca^{2+} channels followed by a deep (15–20 mV) afterhyperpolarization (Fig. 6B). Apart from this afterhyperpolarization, the TMN neurons like to dwell within a small membrane potential range.

Two opposing membrane conductances give the TMN neurons a very typical electrophysiological appearance that allows the identification of a histaminergic neuron impaled in the TMN (Fig. 6C). The response to a hyperpolarizing current injection deviates from a capacitive behavior through activation of a depolarizing current of the h-type (I_h) (552, 553). We find predominantly HCN3 and HCN1 in the rat; the current is not modified by cyclic nucleotides. The return to the resting potential after termination of the current pulse is considerably delayed by activation of two A-type currents. A detailed analysis of

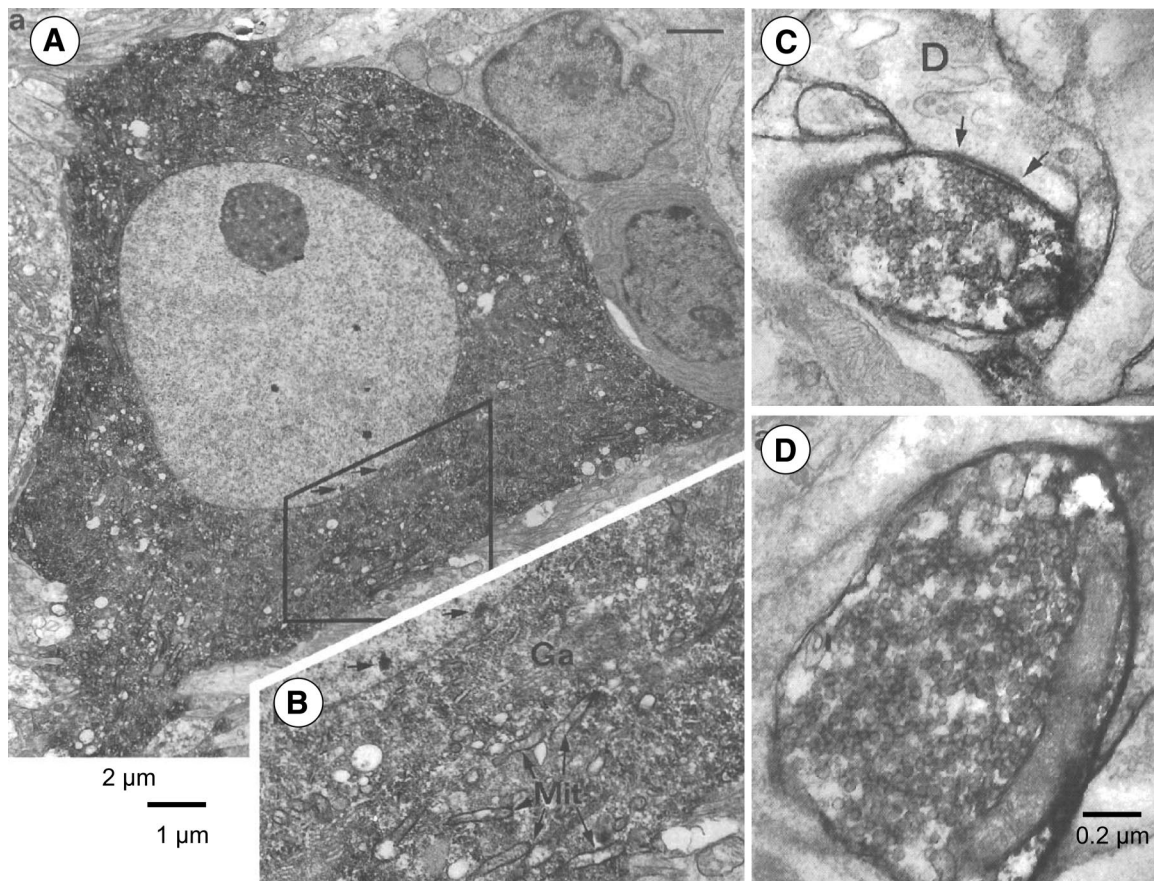


FIG. 5. Electron micrographs of the soma (A and B) and two varicosities (C and D) of histaminergic (HDC-positive) neurons. The large pale nucleus has a prominent nucleolus and no indentations. The cytoplasm contains many organelles. The boxed area shows Golgi apparatus and mitochondria. The varicosities are from the hippocampal part of a coculture with the posterior hypothalamus. C illustrates a bouton establishing an asymmetrical contact on a dendrite (D). D shows the more usual varicose swellings with no contact to synaptic densities. [Modified from Diewald et al. (141).]

the A-type current (I_A) in mouse TMN revealed a subthreshold activation of I_A by fast ramps that imitated the spontaneous depolarizations during pacemaking (296).

Although I_h activated by a hyperpolarization forms the basis for pacemaker cycles in heart and thalamic neurons (552), this function is not attributable to TMN neurons as blocking I_h through Cs^+ does not affect the firing rate; furthermore, the half-maximal activation occurs at about -100 mV (322, 706) while the afterhyperpolarization takes the membrane potential only to -75 to -80 mV (705). This afterhyperpolarization is sufficient to remove inactivation of the fast outward current (I_{Afast} , 4-aminopyridine sensitive) (224) that delays the return to firing threshold and thus slows the firing. A further inactivating K^+ current (I_{Aslow}), which is not blocked by 4-aminopyridine and requires long-lasting hyperpolarizations for removal of inactivation, is unlikely to affect spontaneous firing.

A noninactivating Na^+ current has been identified in TMN neurons (422, 705, 706, 779). This current likely flows continuously even at -70 mV and is sufficient to

drive spontaneous firing. Taddese and Bean (722) were able to assess the role of this sodium current in pacemaking by using the cells own pacemaking cycle as a voltage command. They suggested that the persistent sodium current originates from subthreshold gating of the same sodium channels that underlie the phasic sodium current. None of these intrinsic currents has been found to respond to transmitters or other endogenous neuroactive substances.

Subthreshold Ca^{2+} -dependent depolarizing events contribute to the repetitive firing of histaminergic neurons. These prepotentials are seen when Na^+ -dependent action potentials fail and they persist under tetrodotoxin (TTX). Ba^{2+} converts them to TTX-insensitive full-blown action potentials. They are reduced by Ni^{2+} , indicating a low-threshold type of Ca^{2+} current. These Ca^{2+} currents are likely instrumental in the histamine release from dendrites and the target of autoreceptor-mediated negative feedback on action potential firing (706). Five types of Ca^{2+} currents have been characterized pharmacologically by Takeshita et al. (732) in TM neurons, including N- and

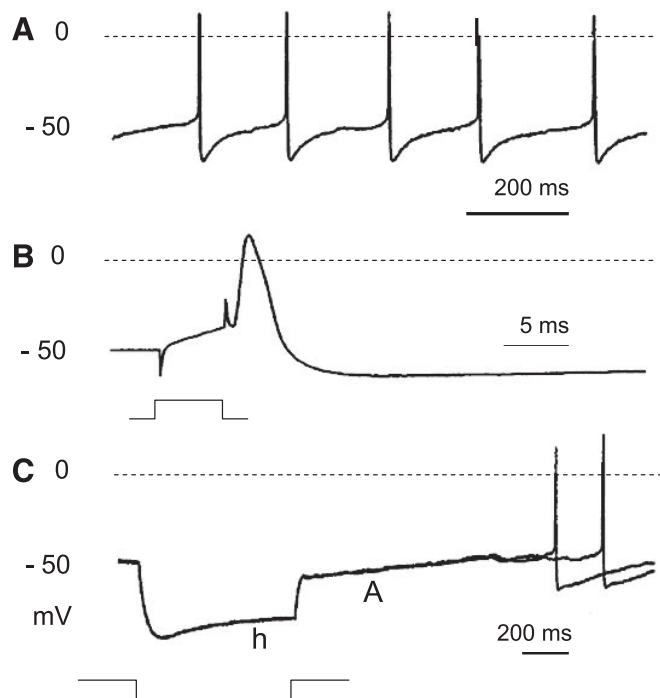


FIG. 6. Intracellular recording from tuberomammillary histaminergic neuron in a slice preparation. *A*: spontaneous firing. *B*: a single action potential, evoked by a depolarizing pulse, showing a relatively long duration with a hunch indicating a Ca^{2+} component followed by an afterhyperpolarization. *C*: response to a hyperpolarizing current injection showing a sag (inward rectification, h) due to activation of an I_h current and a delayed return to the membrane potential after the end of the current injection due to activation of an A-type current. [Modified from Stevens et al. (705).]

P-type currents that were sensitive to histamine H_3 -receptor activation. At the onset of spontaneous firing in vitro, a 20-fold increase of intracellular Ca^{2+} level has been measured (780).

F. Afferent Inputs

Behavioral state-dependent activity of histamine neurons in the TMN is influenced by a variety of neuronal,

humoral, and paracrine signals. The tuberomammillary nucleus receives innervation from the preoptic area of the hypothalamus, the septum, the prefrontal cortex, the subiculum, and the dorsal tegmentum (159, 822, 823, 825, 826), regions that are targets of TMN projections. Stimulation of the diagonal band of Broca, the preoptic area, and the anterolateral hypothalamus can evoke inhibitory postsynaptic potentials (IPSPs) and excitatory postsynaptic potentials (EPSPs) in TMN neurons, suggesting afferents releasing GABA, blocked by bicuculline, and glutamate, blocked by CNQX and APV (840). Monoaminergic and peptidergic fibers reach the TMN neurons and their content meets sensitive receptors after release (163–166, 626, 664, 707).

1. Amino acids

A) GLUTAMATE. Glutamatergic fibers from the cortex and the hypothalamus are present and glutamate excites TMN neurons, which carry both AMPA and NMDA receptors (840), and the neuronal glutamate transporter EAAC1 was detected by immunohistochemistry near histamine neurons (170). Electrical stimulation of lateral preoptic and hypothalamic areas can evoke glutamatergic excitatory potentials in TMN neurons (840). Spontaneous excitatory postsynaptic potentials or miniature excitatory postsynaptic currents (mEPSCs) have not been observed in TMN neurons.

A number of NMDA antagonists increase the synthesis and turnover of histamine, indicating the possibility of an (indirect) inhibitory action through NMDA receptors on TMN neurons which express the NR1, NR2A, and NR2B NMDA receptor subtypes (170). AMPA receptors can be composed of four subtypes: GluR1–4. GluR2 mRNA is most frequently found, followed by GluR1 and GluR4, with the flip splice variant prevailing over flop and GluR3 missing. The presence of GluR2 is responsible for Ca^{2+} impermeability of TMN AMPA receptors (Fig. 7). Expression of GluR4 flop correlates with the fastest desensitization of glutamate-evoked responses and is coordinated with the expression of a K^+ -dependent $\text{Na}^+/\text{Ca}^{2+}$

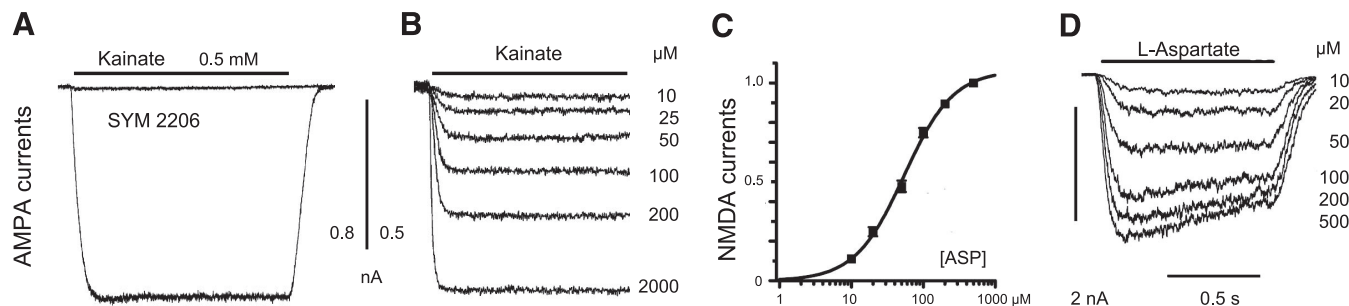


FIG. 7. AMPA- and NMDA-receptor mediated inward currents in isolated TMN histaminergic neurons. *A*: kainate evokes nondesensitizing AMPA-receptor mediated response, blocked by selective AMPA-receptor antagonist. *B*: dose-response relationship, maximal response occurred at 2,000 μM . *C*: normalized dose-response curve for NMDA receptor-mediated responses. *D*: L-aspartate evokes dose-dependent NMDA receptor-mediated responses.

exchanger (NCKX2; single cell RT-PCR data), thus allowing a faster timing pattern of synaptic signals in neurons with this AMPAR subtype (666). Three out of four AMPA receptor subunit pre-mRNAs undergo editing by adenosine deaminases acting on RNA (ADAR1–3). In TMN neurons, editing determines desensitization properties (665).

B) GLYCINE AND TAURINE. Glycine inhibits a subpopulation of histaminergic neurons (668), but glycinergic fibers in the posterior hypothalamus are uncertain. Maximal glycine-evoked currents could reach 3 nA, on the average 40% of the maximal GABA-evoked currents in large (25 μ m) TMN neurons (Fig. 8). In smaller (<20 μ m) HDC mRNA-positive neurons, glycine responses are small or absent. Neurons between 8 and 15 μ m diameter encountered in the rat TMN are HDC mRNA negative. Taurine, an osmolyte that can reach relevant concentrations in the extracellular space, gates strychnine-sensitive glycine receptors and GABA_A receptors. Immunocytochemistry demonstrated a uniform distribution of taurine and the taurine transporter protein in histaminergic neurons (unpublished observations). Taurine efficacy at GABA_A receptors is independent of GABA_A receptor composition, and taurine will thus, in contrast to GABA, equally inhibit (and protect from overexcitation) a large range of neurons.

C) GABA. GABAergic inputs come from several mostly hypothalamic locations, functionally prominent with respect to sleep-waking regulation is the innervation from the ventrolateral preoptic (VLPO) area which fires high during sleep and thus suppresses the firing of histamine neurons (159, 636, 678, 703). GABA_AR are quite heterogeneous among histamine neurons; three groups with different GABA sensitivities have been identified, depending on the expression of the γ -subunit of the ionotropic GABA_AR (669). A genetic approach has indicated that α 2- and β 3-containing GABA_AR are most relevant for sleep (620). The sedative component of general anesthetics (e.g., propofol) (511) is attributed to actions on GABAergic afferents to the TM nucleus, with one key to this action being

the low expression of the GABA_AR ϵ -subunit (667). Cessation of histaminergic neuron firing is associated with the loss of consciousness. The GABAergic inputs to the TMN are under feedback control of GABA_BR: no postsynaptic GABA_BR-mediated effects but GABA_AR-mediated synaptic potentials are strongly suppressed by baclofen, a GABA_BR agonist (708).

2. Biogenic amines

Aminergic and cholinergic nuclei send projections to the TMN; they are functionally excitatory and use a variety of mechanisms. Histamine inhibits histaminergic neurons through H3-autoreceptors which exhibit constitutive activity (34, 200, 496).

A) ACETYLCHOLINE. A nicotinic fast desensitizing action occurs through α 7-type acetylcholine receptors (781, 783). These bungarotoxin-sensitive receptors are likely not involved in synaptic transmission but represent a sensor for the central waking actions of nicotine. Choline has been put forward as the natural ligand in TMN (780, 782). It binds only to the α 7-type receptor with an EC₅₀ of 1.6 mM (EC₅₀ for ACh: 0.13 mM) (18). Muscarinic actions have not been detected on TMN neurons in vitro. Thus pharmacological modulation of histamine release via M1 or M3 heteroreceptors in vivo (589) occurs presumably on histaminergic axons.

B) CATECHOLAMINES. The TMN receives input from the noradrenergic cell groups including the locus coeruleus. Norepinephrine does not affect histaminergic neurons directly but effectively controls GABAergic input through α 2-adrenoreceptors mediating an inhibition of IPSCs: evoked GABAergic IPSPs are reduced by norepinephrine and clonidine but not isoproterenol while exogenously applied GABA responses remain unaffected (707). Dopamine also excites histamine neurons through D2 receptor activation (671).

C) SEROTONIN. Serotonin excites the histaminergic neurons of the rat through activation of Na⁺/Ca²⁺ exchange (NCX) (166, 664, 672). This electrogenic transporter has to let 3 Na⁺ enter the cell to expel 1 Ca²⁺, resulting in a depolarization and excitation in the absence of any conductance change. Serotonin 2C receptors undergo post-transcriptional gene modifications, and the editing status can predict psychiatric disease (647). Combinations of unedited and edited points on mRNA species generate 14 different isoforms of the 5-HT_{2C}R. None of the 5 editing sites (A–D) depends on the known ADAR enzymes in TMN neurons, which are always edited at A and variably edited at B–D sites. Formation of the fully edited 5-HT_{2C}R, which are less responsive to agonists, is prevented; there is a negative correlation between the editing of C and D sites (665).

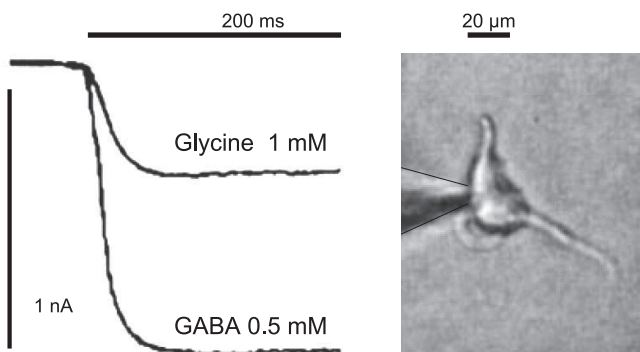


FIG. 8. Maximal responses of an isolated TMN neuron to glycine and GABA (chloride ion currents). The large recorded neuron on a patch pipette is illustrated. [Modified from Sergeeva et al. (668).]

3. Purines (nucleotides, nucleosides)

Nucleotides excite histaminergic neurons through ionotropic and metabotropic receptors. There is no evidence for synaptic release onto histamine neurons, but these excitations may be relevant for homeostatic sleep regulation (see below). ATP-induced inward currents in neurons from the tuberomammillary region were first reported by Furukawa et al. (188).

ATP evokes fast nondesensitizing inward currents in TMN neurons. Single-cell RT-PCR and pharmacological analysis revealed P2X₂ receptors as the major receptor type that occurs in all TMN neurons (796); five further types are expressed rarely. Zn²⁺ acts as a bidirectional modulator of P2X₂ receptors (797). Zn²⁺ potentiation of ATP responses is caused by slowing ATP dissociation from the receptor, while inhibition at higher concentrations of Zn²⁺ is related to suppression of gating. ATP, ADP, UTP, and 2MeSATP excite TMN neurons through metabotropic receptors; P2Y₁ and P2Y₄ are prevailing (670). Semiquantitative real-time PCR revealed a developmental downregulation of these receptors. Immunohistochemistry demonstrated neuronal and glial localizations of P2Y₁ receptors (670).

ATP is broken down to adenosine extra- and intracellularly: adenosine which inhibits many neurons and synaptic transmissions has no effect on TMN firing or TMN inputs (670). The tuberomammillary nucleus displays a very strong expression of adenosine deaminase, which has led to the suggestion that it may also use adenosine as a transmitter. So far, such a role of adenosine is elusive; there is no evidence for synaptic release of this nucleoside, but it is sedative through adenosine A₁ receptors. A_{2A} receptors have also been implicated in sleep regulation, through enhancement of the GABAergic inhibition of histamine neurons (262, 643), probably as a consequence of prostaglandin D₂ (PGD) release (for review, see Refs. 251, 274). Microdialysis of adenosine A₁- and A₂-selective agonists in the lateral preoptic area induced waking and sleep, respectively, presumably by inhibiting the GABAergic neurons that project to the TMN through A₁ receptors and exciting them through A_{2A} receptors. An adenosine transport inhibitor (NBTT) which leads to extracellular adenosine accumulation also causes sleep (17, 468). Adenosine accumulates during wakefulness and is considered as a sleep pressure substance (275, 583); it prevents overexcitation and neurotoxicity and acts as an endogenous anti-epileptic (237).

4. Peptides

Many peptides function as signaling molecules in the hypothalamus where they are involved in endocrine and homeostatic functions. They can be coexpressed and differentially released with "classical" neurotransmitters;

in many neurons however, they represent the main transmitter or hormone.

A) GALANIN. Galanin is coexpressed in histaminergic neurons of rodents (7, 361, 373) (not in the human TMN, Ref. 766) and in the GABAergic inputs to them (678). Galanin inhibits TMN neuron firing (650) and may participate in both the autogenic (feedback) inhibition and the extrinsic inhibition from the VLPO. In addition, galanin has been shown to act on TMN axons on autoreceptors located on the varicosities (33). Galanin also exerts neurotrophic, antiepileptic, sleep-propensating, and orexigenic actions.

B) OREXIN/HYPOCRETIN. Orexin/hypocretin-containing neurons are neighbors of the histamine neurons; the nuclei intermingle partially and represent a functional entity. Degeneration of hypocretin neurons is causal in most cases of narcolepsy, with excessive daytime sleepiness and cataplexy (680, 851). Hypocretins maintain wakefulness, particularly in the context of metabolic challenges, and are thought to organize a flip-flop sleep switch that prevents unwanted frequent transitions between behavioral states (636). Both hypocretins (1 and 2, also known as orexin A and B) excite histamine neurons through the Hcrt2 receptor and activation of NCX (163, 165, 166, 664) (Fig. 9). This action is secondary to a rise in intracellular Ca²⁺ that probably comes from both extra- and intracellular sources. Hypocretin neurons also express dynorphin, which can contribute to the excitation of histaminergic neurons by suppressing inhibitory GABAergic in-

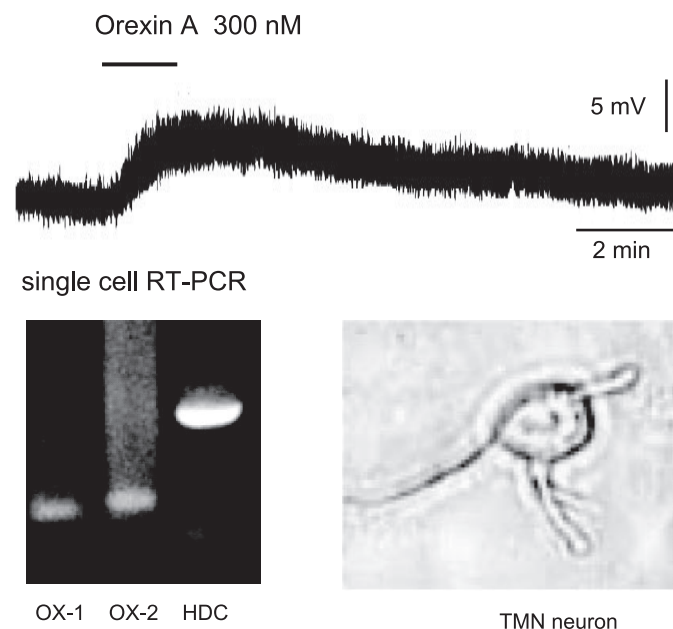


FIG. 9. Depolarization of a TMN neuron by orexin-A/hypocretin-1 under tetrodotoxin. Single-cell RT-PCR revealed expression of both orexin/hypocretin receptors in this HDC positive (histaminergic) neuron. [Modified from Eriksson et al. (166).]

puts (164). TMN neurons *in vivo* remain active during cataplectic attacks in narcoleptic hypocretin-2 receptor-deficient dogs (305), and both the effects of hypocretin on vigilance (272) and food intake (310) require H1R activation. H1R-KO mice have lower hypocretin levels (in contrast to various other KO mice) (415).

C) CORTICOTROPIN RELEASING HORMONE, GLUCAGON-LIKE PEPTIDE-1, LEPTIN, NEUROPEPTIDE Y, GHRELIN, THYROTROPIN RELEASING HORMONE. Morphological and systemic data suggest TMN-dependent control of leptin actions on food intake. Leptin, the hormone from fat that controls food intake and body weight, has no obvious effect on TMN neurons, but the latter are secondary targets and mediators of leptin actions in the brain (758). A study of the interactions of glucagon-like peptide-1 (GLP-1), corticotropin releasing hormone (CRH), and histamine concluded that CRH or hypothalamic neuronal histamine mediates the GLP-1-induced suppression of feeding behavior, that CRH mediates GLP-1 signaling to neuronal histamine, and that a functional link from GLP-1 to neuronal histamine via CRH constitutes the leptin-signaling pathway regulating feeding behavior (214). Neuropeptide Y (NPY)-containing fibers are found close to histaminergic neurons (734), and NPY indirectly affects histamine release (286). The appetite-stimulating stomach-derived ghrelin inhibits a potassium channel (Kir3) in cultured TMN neurons (39). Thyrotropin releasing hormone (TRH) reduces food intake (215) and sleeping time in rats and combats excessive sleepiness in canine models of narcolepsy (612). The majority of the TMN neurons are excited by TRH (673).

D) NOCICEPTIN, DYNORPHIN, AND SUBSTANCE P. Nociceptin (Orphanin FQ) is widely expressed in the brain, particularly the arcuate nucleus, and occurs in many fibers near histaminergic somata in the TMN region. It strongly inhibits (hyperpolarizes) TMN neurons at the postsynaptic level by activating an inwardly rectifying K⁺ conductance (Fig. 10). Morphine (a μ -receptor agonist) excites TMN neurons through disinhibition, by inhibiting GABAergic neurons (165). The κ -agonist dynorphin has no effect. Substance P-immunoreactive (SP-IR) terminals make synaptic contacts with the somata, somatic spines, and dendrites of histaminergic neurons (733).

5. Metabolic signals (glucose, lipids, CO₂)

Insulin-induced hypoglycemia activates TMN neurons of the E4 and E5 subgroup in the tuberomammillary region (475). In mice deficient in ApoE, a lipoprotein receptor, chronically decreased histamine levels and reduced histamine release in the amygdala might contribute to increased anxiety (785). Estrogen receptors are expressed in the human tuberomammillary nucleus, and their expression levels vary in relation to metabolic activity, sex, aging, and Alzheimer's disease (287). Prostaglandin E₂ activates the TMN via the EP4 receptor to induce

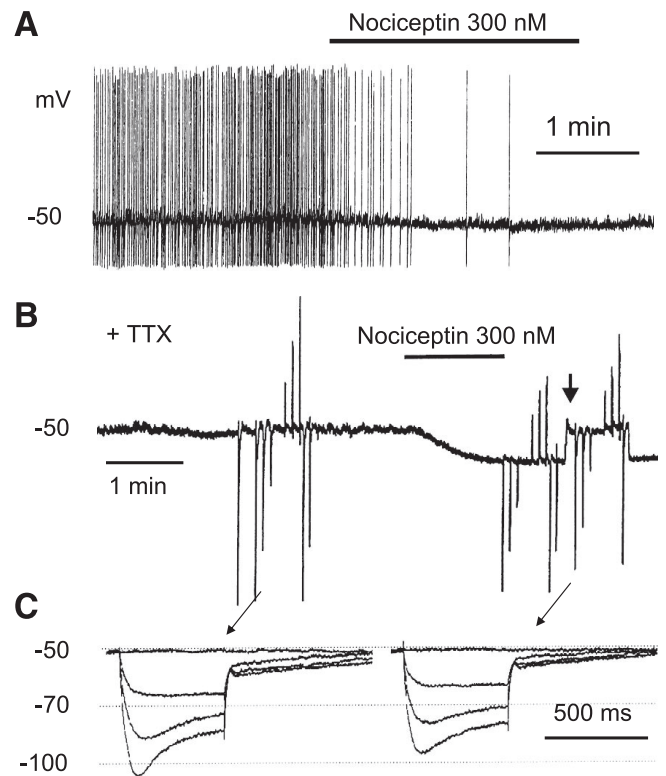


FIG. 10. Inhibition of TMN histaminergic neuron by nociceptin. A: depression of firing and hyperpolarization. B: hyperpolarization under tetrodotoxin in the absence of action potentials. C: voltage responses to hyperpolarizing current injection reveal an increased (potassium) conductance. At the vertical arrow, the voltage was manually clamped to the initial value, -50 mV. [Modified from Eriksson et al. (165).]

wakefulness in rats (273). Endocannabinoids increase histamine release selectively in the TMN through CB1R but independent from modulation of GABAergic transmission (100). Histaminergic neurons may also be involved in CO₂-mediated arousal (306, 527).

G. Histaminergic Pathways and Targets

Although both HDC and histamine are present in TMN somata and axon varicosities, the histamine antibodies stain the fibers better than those against HDC. Similar basic projection patterns of histaminergic neurons have been described for several species, but there are significant quantitative differences with regard to the innervation density of the target regions. The projection pattern in guinea pig is closer to that in the treeshrew than to that in mouse and rat. Since the latter rodents have been used in the majority of electrophysiological and behavioral studies, their innervation pattern is detailed below. Multifold arborizing axons reach the entire central nervous system through two ascending and one descending bundle (362, 551, 690, 804, 824). (Figs. 1 and 11). One ascending pathway travels at the ventral surface of the

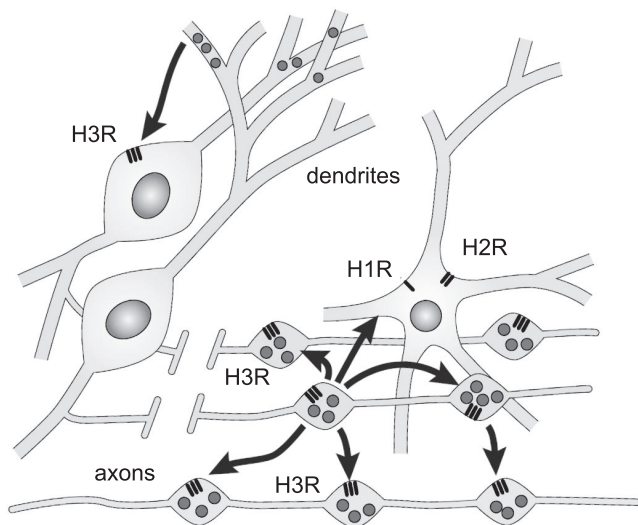


FIG. 11. Tuberomammillary histaminergic neurons and their targets. H3 receptors are on their somata, dendrites, and axons, as well as on the axons of other cells. H1 and H2 receptors are on a target cell body. Release of histamine is from dendritic and axonic vesicles. [Modified from Haas and Panula (235).]

median eminence to the hypothalamus, the diagonal band, the septum and the olfactory bulb, hippocampus, and cortex, and the other leaves the TMN dorsally and runs along the third ventricle to thalamus, basal ganglia, hippocampus, amygdala, and cortex. The descending path goes with the medial longitudinal fasciculus to brain stem and spinal cord. There seems to be no topological correlation between the location of TMN somata and their projections. Tracing studies have shown that histaminergic fibers are extensively crossing (mainly in the supra-chiasmatic and supramammillary decussations), and many neurons branch to more than one of the initial pathways (161, 548, 548, 726).

The highest density of histaminergic fibers is seen in the hypothalamus, fiber bundles are passing through, and most parts of this structure are densely innervated. The anterior periventricular, retrochiasmatic, supraoptic decussation, and laterobasal regions display the highest histamine immunoreactivity; dense networks of histaminergic fibers are found in the medial preoptic, periventricular, supraoptic, and supra-chiasmatic nuclei. A medium density is found in the paraventricular, dorsomedial, ventromedial and arcuate nuclei. In the posterior hypothalamus, histaminergic fibers often make close contact to the brain surface.

The septal nuclei and those of the diagonal band receive a very strong histaminergic innervation. A dense network of fibers passes through and innervates the supramammillary nucleus that contains glutamatergic neurons projecting to cortical areas. The ventral tegmentum and the dopaminergic nuclei (substantia nigra and VTA) receive moderate to dense histaminergic input. This is

true also for the tectum, with a particularly interesting basketlike innervation pattern of the mesencephalic trigeminal nucleus. Some neurons in the pontine central gray also display immunoreactive terminal-like structures (548). Furthermore, the mesencephalic reticular areas giving rise to the ascending reticular activating system and the aminergic nuclei (the noradrenergic locus coeruleus and the serotonergic raphe nuclei) are moderately innervated. Histaminergic fibers descend further to the spinal cord.

In the olfactory bulb, the area surrounding the glomeruli and the olfactory nuclei receive a moderate innervation. The fiber density in the striatum varies; moderate densities are observed in anterior parts of the dorsal striatum and in the nucleus accumbens. The periventricular and the posterolateral thalamic nuclei receive a moderate innervation too: paraventricular nucleus, medial habenula, and medial geniculate nucleus. Lower densities are seen in further thalamic nuclei, including lateral habenula and lateral geniculate nucleus. Most neocortical and allocortical areas contain moderately dense or sparse histaminergic fibers, with an emphasis on the superficial layers. Histaminergic fibers enter the hippocampus through both an anterior and a posterior pathway and reach a moderate density in the basal parts of cornu ammonis, subiculum, and dentate gyrus. Moderate fiber densities are also found in parts of the amygdala.

VII. RECEPTORS

A. Metabotropic Receptors

Four metabotropic histamine receptor types (H1R–H4R) have been cloned so far. H1–H3R are expressed in abundance in the brain. H4R occurs mainly in peripheral tissues (135). All metabotropic histamine receptors (H1R–H4R) belong to the rhodopsin-like family of G protein-coupled receptors (GPCR) (255, 393, 651) (<http://www.gpcr.org>). Each receptor consists of seven large transmembrane-spanning elements with prototypic domains determining agonist binding specificity and activation (42, 307, 394, 404), G protein coupling and constitutive activity (40, 43, 200, 688), as well as covalent modifications (e.g., through phosphorylation by protein kinases), homo- and heterodimerization, trafficking and membrane anchoring, as well as receptor sensitization and desensitization (e.g., through agonist-induced internalization) (377). A high degree of molecular and functional heterogeneity achieved through different transcriptional and posttranscriptional processing (splice variants) is prototypic for the H3R, which is largely confined to the nervous system (393).

1. H1 receptors (H1R)

The gene encoding the human H1R, which is a 56-kDa 487-amino acid peptide, is located on chromosome 3p25

(see Table 1). Using combined site-directed mutagenesis and molecular modeling, Leurs et al. (307) characterized important steps in the activation of the human histamine H1R involving specific residues that are conserved among rhodopsin-like GPCRs.

The signal transduction of H1R (395) is typical for and convergent with that of other $G_{\alpha_{q/11}}$ protein-coupled receptors (40, 83, 163, 659). This includes activation of phospholipase C (PLC) promoting 1) inositol trisphosphate (IP_3)-dependent release of Ca^{2+} from intracellular stores and 2) diacylglycerol (DAG)-sensitive activation of protein kinase C (PKC), which facilitates capacitive Ca^{2+} entry through voltage-dependent calcium channels (VDCC), cation channels of the transient receptor potential channel family (TRPC) (83, 672), and stimulation of a NCX (163, 664). Other effector pathways of H1R include production of arachidonic acid (AA), nitric oxide (NO), and cGMP (395, 588, 611, 691) through pertussis toxin-sensitive G_i/G_o protein-mediated activation of phospholipase A_2 (PLA_2), $[Ca^{2+}]_i$ -dependent NO synthases, and NO-dependent guanylate cyclases (GC), respectively. Importantly, H1R activate AMP-kinase, a checkpoint in the control of energy metabolism (336), and nuclear factor-kappaB (NF- κ B) (43), a key transcription factor controlling genomic imprints and readout.

H1R are found throughout the whole body and nervous system with considerable variations among species (101). H1R density does not always match that of the less variable histaminergic innervation, and studies using

$[^3H]$ mepyramine binding indicate that a major portion of H1R may be associated with nonneuronal elements such as glia, blood cells, and vessels. Particularly high densities are found in brain regions concerned with neuroendocrine, behavioral, and nutritional state control, like the hypothalamus, aminergic and cholinergic brainstem nuclei, thalamus, and cortex. In human brain, the highest $[^3H]$ mepyramine binding is found in the cerebral cortex and the infralimbic structures (448) in keeping with the mapping of H1R using $[^{125}I]$ iodobolpyramine autoradiography in the guinea pig (66). With availability of appropriate PET tracers ($[^{11}C]$ pyrilamine and $[^{11}C]$ doxepin) in the early 1990s (838), H1R distribution and occupancy in humans have also been mapped using functional imaging techniques (836) to study the sedative properties and blood-brain barrier (BBB) permeability of H1R antihistamines (742), aging (837), and neuropsychiatric disorders, such as Alzheimer's disease, schizophrenia (294), and depression (325), in all of which H1R binding was found lower than in age-matched healthy controls.

Histamine through H1R excites neurons in most brain regions, including brain stem (45, 367, 407) (Fig. 12), hypothalamus, thalamus (462, 694, 855), amygdala, septum (213, 828), hippocampus (445, 659), olfactory bulb (299), and cortex (603). Activation of K^+ channels through an increase of $[Ca^{2+}]_i$ by H1R decreases cell excitability and inhibits cell firing in hippocampal pyramidal neurons (659). In glia cells (341, 805) and cerebellar Purkinje neurons (340), the activation of these channels relies on PLC activation and IP_3 -

TABLE 1. *Molecular and functional properties of histamine receptors in the nervous system*

Properties	H1R	H2R	H3R	H4R
Chromosome gene locus	3p25	5q35.2	20q13.33	18q11.2
Protein (amino acids)	487	359	445	390
G protein isoforms	$G_{q/11}$	G_{α_s}	$G_{i/o}$	$G_{i/o}$
Constitutive activity	+	+	++*	?
Signal transduction	PLC IP_3 , DAG Ca^{2+} , PKC AMPK, NF- κ B	AC cAMP, PKA CREB	AC ↓ cAMP ↓ MAPK Akt/GSK3	AC ↓ cAMP ↓ MAPK
Effector pathways	TRPC $I_{K_{leak}}$ ↓	I_h (HCN2) I_{AHP} ↓	I_{Ca} ↓	Cytoskeleton
Cellular function	Postsynaptic excitability and plasticity†	Postsynaptic excitability and plasticity	Presynaptic transmitter release‡ and plasticity	?
Systemic function	Behavioral state and reinforcement (novelty, arousal) Working memory Feeding rhythms Energy metabolism Endocrine control	Learning and memory (consolidation)	Numerous CNS functions,‡ cognition, emotion, learning, and memory Blood-brain barrier control	Chemotaxis
Pathophysiology	Disorders of sleep, mood, memory, eating, and addiction Pain and neuroinflammation	Schizophrenia Pain and neuroinflammation	Disorders of sleep, mood, memory, eating, and addiction pain and neuroinflammation	?

See text for definitions. *High degree of constitutive activity. †In synergy with H2R. ‡Autoreceptor on histaminergic neurons and heteroreceptor on aminergic, glutamatergic, GABAergic, and peptidergic neurons.

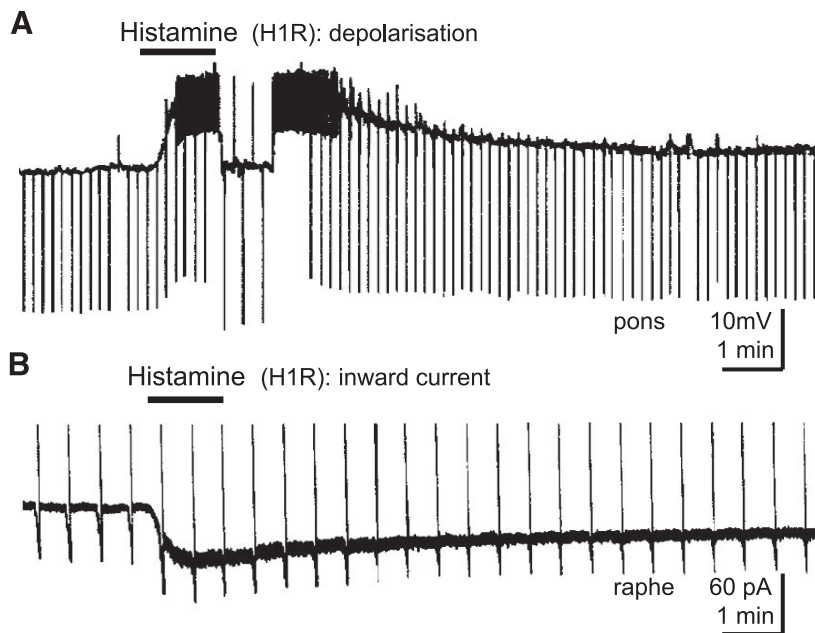


FIG. 12. Histamine H1R-mediated actions on brain stem neurons. *A*: depolarization of a medial pontine reticular formation neuron. Vertical strokes are from negative current pulses showing a larger voltage response during histamine at comparable voltage level (manual clamp) indicative of resistance increase due to closure of a (potassium) channel. *B*: inward current accompanied by an increased membrane noise indicating channel openings (likely of the TRPC type) in a dorsal raphe neuron. [Modified from Brown et al. (83).]

mediated release of Ca^{2+} from internal stores. The complex H1R signaling includes bidirectional and synergistic effects (40, 129, 197, 764); for example, H1R oppose or amplify H2R actions depending on the timing and context of receptor activation and may serve as a coincidence detector for $G_s\alpha$ -/PKA-dependent signaling (40, 50, 197, 461, 659).

Global loss of H1R function in KO mice (257, 271, 453) produces immunological, metabolic, and behavioral state abnormalities similar to those observed in HDC-KO animals (556). All H1R antihistamines function as inverse agonists, i.e., stabilizing the receptor in its inactive state (42, 307, 394); the term *H1R antagonist* is thus erroneous. Classic antihistamines act at H1R (684) with well-known sedative properties (67, 407, 603). Many antidepressants or antipsychotics also bind to the H1R (336, 611).

2. H2 receptors (H2R)

The gene encoding the human H2R, which is a 40-kDa 359-amino acid peptide, is located on chromosome 5q35.5 and exhibits strong sequence homology (83–95% identity) with that in guinea pig, mouse, rat, and dog (359, 765). H2Rs exhibit constitutive activity, and inverse agonism of H2R antagonists accounts for upregulation of spontaneously active H2R, which may underlie the development of tolerance after prolonged clinical use (688). The COOH terminus of the H2R plays a role in agonist-induced internalization, although the protein-protein interactions are unknown (377). Interestingly, the absence of histamine downregulates H2R expression but not H1Rs in a tissue-specific manner (175). Development of fluorescent histamine receptor ligands may shed light on these phenomena in the future (441).

Distribution of H2R in the rodent brain is widespread but more consistent than that of H1R with histaminergic projections, indicating that H2R mediate a larger number of postsynaptic actions of histamine (617, 792). However, colocalizations of H1R and H2R in some areas may account for synergistic interactions between these receptor subtypes (40, 50, 197, 461, 659). Particularly dense labeling of H2R is found in the basal ganglia, amygdala, hippocampus, and cortex, where they display a laminar distribution.

H2R couple to $G_s\alpha$ proteins to stimulate adenylyl cyclase and increase intracellular cAMP (40, 50, 197, 764), which activates protein kinase A (PKA) and the transcription factor CREB, all of which are key regulators of neuronal physiology and plasticity (35, 234, 462, 562, 563, 659). cAMP can directly interact with hyperpolarization activated cation channels I_h (HCN2) (462, 563). Through H2R activation and PKA-dependent phosphorylation, histamine blocks a Ca^{2+} -activated potassium conductance (small K) responsible for the accommodation of firing and the long-lasting (seconds) afterhyperpolarization following action potentials in pyramidal cells (234, 562), as well as fast spiking through modulation of Kv3.2-containing potassium channels in interneurons (35). Independent of either cAMP or $[\text{Ca}^{2+}]_i$ levels, H2R also inhibit PLA_2 and release of arachidonic acid, which likely account for the opposing physiological responses elicited by H1R and H2R in many tissues (764).

Mice deficient in H2R function exhibit selective cognitive deficits along with an impairment in hippocampal LTP (127) and with abnormalities in nociception (479, 480) and gastric and immune functions (748). H2R antag-

onists are widely prescribed for therapy of gastric disorders and seem to have antitumor activity (391). Some antidepressants also have H2R antagonistic properties (219) and a few reports suggested efficacy of H2R antagonists in schizophrenia (see below).

3. H3 receptors (H3R)

The H3R was discovered in 1983 by the group of J.-C. Schwartz in Paris (32). Lovenberg et al. reported its cloning in 1999 (426) (616, 740, 741). The gene (*Hrh3*) encoding human H3R, a 70-kDa 445-amino acid peptide, is located on chromosome 20q13.33. Featuring two or three introns and many splice variants, the *Hrh3* gene, in contrast to *Hrh1* and *Hrh2*, yields a large number of receptor isoforms with different distribution and pharmacology (41, 148, 425; for review, see Refs. 34, 393, 560). H3R negatively couple through pertussis toxin-sensitive $G_{i/o}$ proteins to N- and P-type Ca^{2+} channels (732) and to adenylyl cyclase (493, 761). Through extensive cross-talks with other GPCRs, they can also engage $G_{q/11}$ signaling and activate PLA_2 , Akt/GSK3 (62), and MAP kinase pathways (205), all of which play important roles in axonal and synaptic plasticity and a variety of brain disorders (see sect. xi).

A striking property of H3R is their high degree of constitutive activity in vivo (200, 496, 725). While constitutive activity of GPCR in artificial expression systems is common, it is a rarely observed phenomenon in vivo, except for H3R (496). The existence of ligand-directed active states different from, and competing with, constitutively active H3R states defines a novel pharmacological entity referred to as protean agonism with important functional and therapeutic implications (200, 393, 696). As autoreceptors on somata, dendrites, and axons of TMN neurons, constitutively active H3R (34) inhibit cell firing (705), as well as histamine synthesis and release from varicosities (31, 493, 761). As presynaptic heteroreceptors, H3R control the release of a variety of other transmitters, including biogenic amines (575, 646), acetylcholine (34, 61), glutamate (82, 146), GABA (300, 831), and peptidergic systems (574, 575) (Figs. 11 and 13).

A detailed mapping of H3R and its gene transcripts using autoradiography with (*R*)-[3H]- α -methylhistamine or [125I]iodoproxyfan in rats (573, 580), as well as immunohistochemical studies in mice (103) revealed that H3R, in keeping with their role as auto- and heteroreceptors, are heterogeneously distributed among areas known to receive histaminergic projections. High densities are found particularly in anterior parts of the cerebral cortex, hippocampus, amygdala, nucleus accumbens, striatum, olfactory tubercles, cerebellum, substantia nigra, and brain stem. In the TMN, H3R reside on perikarya of histaminergic neurons.

Loss of H3R function in KO mice is associated with behavioral state abnormalities, reduced locomotion (762), a metabolic syndrome with hyperphagia, late-onset obesity, increased insulin and leptin levels (759, 848), and an increased severity of neuroinflammatory diseases, in keeping with data from genetic linkage studies (749). Atypical neuroleptics such as clozapine bind to H3R. With its unique pharmacological properties, the H3R is a major target for development of drugs against various disorders of the brain (393, 560) (see sect. xi).

4. H4 receptors (H4R)

The recently cloned H4R receptor exhibits molecular homology and pharmacology similar to H3Rs (201) but is expressed mainly in peripheral cells and tissues, such as blood, spleen, lung, liver, and gut (73, 494), although it may be present in some parts of the brain as well. H4R emerges as a promising drug target in inflammation (135, 393, 494); 4-methylhistamine is a selective agonist at the H4R (404, 494).

B. Ionotropic Receptors

Histamine activates chloride conductances in hypothalamus (250) and thalamus (390). On oxytocin neurons in the supraoptic nucleus, this effect is blocked by picrotoxin (not bicuculline) and H2R antagonists, not mediated by a G protein. TMN stimulation evokes fast IPSPs that

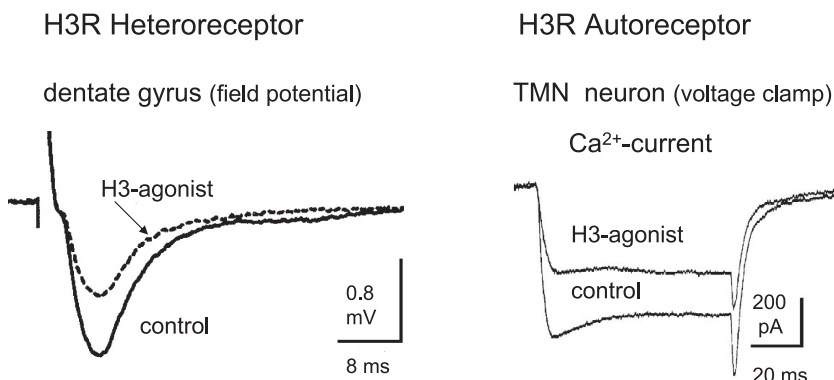


FIG. 13. Histamine H3R actions on heteroreceptor and autoreceptor in hippocampus and hypothalamus. Glutamatergic field potential in dentate gyrus and Ca^{2+} current in histaminergic neuron are reduced. [Modified from Haas and Panula (235).]

reverse at the chloride equilibrium. Hatton and Yang (250) have suggested an ionotropic action and ruled out GABA release from TMN axons, but in spite of their scholarly discussion, the receptor identity remains elusive. In thalamic perigeniculate GABAergic interneurons that are surrounded by histaminergic fibers, histamine also evokes an inhibitory chloride conductance mediated by H2R but not cAMP (390). This would also rule out the gating of Cl^- channels by cAMP directly. So far, no histamine-gated chloride channel has been seen in vertebrate tissues; the evidence is indirect and circumstantial. Several reports have shown "GABAergic activity" of imidazole compounds (231), in particular imidazole-derived H2R antagonists (94, 379).

The "ionotropic histamine receptor" is likely a GABA_A -receptor with a particular subunit composition. Among the many sites for allosteric modulators of the GABA_A receptor, there may also be a histamine-sensitive one. This would not be entirely surprising in light of the known modulation of NMDA receptors by histamine (see below). Very recently, Saras et al. (637), using cRNA expression in *Xenopus* oocytes, have reported that histamine can directly open homomultimeric channels composed of GABA_A β -subunits in which GABA is only a weak partial agonist. In heteromultimeric channels composed of $\alpha 1\beta 2$ or $\alpha 1\beta 2\gamma 2$ subunits, histamine is not an agonist but potentiates the GABA response. These effects have yet to be shown in native neurons. We have not observed such positive modulations in both mature and immature hippocampal and hypothalamic neurons ($n = 50$; Sergeeva, unpublished observation).

1. Polyamine-binding site of NMDA receptors

A second messenger-mediated modulation of ionotropic receptors is common for several transmitters: facilitation of NMDA receptors through PKC and a reduction of the Mg^{2+} block have been described as a result of H_1 receptor activation (561). However, histamine also directly facilitates NMDA receptors and enhances excitatory transmission through their polyamine modulatory

site (54, 54, 798). This action is occluded by spermidine (798) and is pH sensitive (641, 844). In a slightly acidified environment (pH 7.0) but not at pH 7.4, the late NMDA component of extra- and intracellularly registered EPSPs in hippocampal slices is enhanced by histamine. Such shifts in pH occur during intense nervous discharges, e.g., in epileptic tissue or following tetanic stimulation, and in hypoxic conditions. The effect is not mediated by any of the known histamine receptors but can be mimicked by the histamine metabolite 1-methylhistamine and is selective for the NR2B subunit of the NMDA receptor (818) (Fig. 14), which plays a central role in synaptic plasticity. This direct action of the diamine histamine on the polyamine site of the NMDA receptor might have been predicted from the cross-reaction histamine-spermidine in the early attempts with histamine-fluorescence histology (218).

VIII. ACTIONS IN THE NERVOUS SYSTEM

Like other aminergic cells, the histamine neurons act on their own somata, dendrites, and axon varicosities through autoreceptors (H3R). Postsynaptic targets include somata and axon varicosities of many neurons and glial cells all over the nervous system (Fig. 11).

A. Peripheral Nervous System

1. Vegetative nervous system

Histamine release from mast cells, enterochromaffin cells, glomus cells in the immune, gastrointestinal, and chemosensory systems targets parasympathetic nerve endings in the periphery (298). In the nucleus tractus solitarius (see below) and other central representations of the parasympathicus (10), histamine modulates neuronal activity through H3R (124, 853). Histamine neurons in the TMN are part of the central representations of the sympathicus (102, 371, 635) and control sympathoadrenal outflow through H3R (102). Moreover, histamine modu-

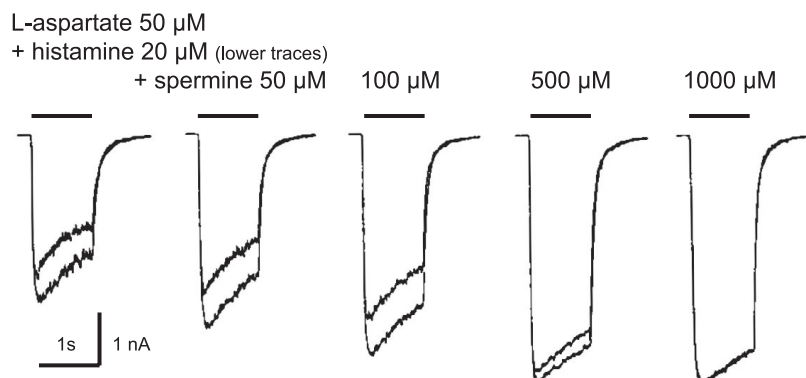


FIG. 14. Histamine, spermine, and NMDA receptor-mediated currents. Histamine and spermine potentiate an aspartate-evoked NMDA receptor-mediated inward current; at increasing concentrations of spermine, the histamine-evoked potentiation is occluded. This histamine action occurs at the polyamine binding site of the NMDA receptor (NR1B subunit). [Modified from Vorobjev et al. (798).]

lates neuronal activity in sympathetic ganglia and the adrenal gland (75, 112, 681) and is a suspect cotransmitter in the sympathetic nervous system (398). In sympathetic ganglia and adrenal medulla, histamine is found in cells with large granular vesicles, in the so-called SIF (small intensely fluorescent cells) of the ganglia, and chromaffin cells of the adrenal gland (245, 246). Histamine can act in a paracrine/endocrine fashion in these structures (111, 809).

2. Somatosensory system (nociception and itch)

Cutaneous itch is mediated by C-fibers distinct from those subserving pain sensation (278) (see sect. xi). These very thin fibers do not belong to the polymodal mechanical and heat nociceptors. They are insensitive to mechanical stimulation but respond to pruritogens, in particular histamine that is the main mediator of the itch in urticaria or following insect bites (278). Heterosynaptic H3R on CGRP-expressing dorsal root ganglia and periaxonal, peptidergic A δ fibers may modulate high-threshold mechanical nociception (93).

B. Spinal Cord and Brain Stem

Histamine-immunoreactive nerve fibers in the spinal cord originate from the posterior hypothalamus, and the fiber projection is more extensive in higher mammalian species (544). Early microelectrophoretic (microionophoretic) experiments had revealed mostly inhibitory actions of histamine in the spinal cord and brain stem of the cat (23, 231, 266, 571) and the hemisectioned spinal cord of the toad (746). A recent study combining whole cell recording in spinal (preganglionic) sympathetic neurons with single-cell RT-PCR revealed mRNA expression for H1R and a H1R-mediated depolarization through block of a K⁺ conductance (815). Like other amines, ionophoretically applied histamine excites most of the neurons in the area postrema (97), a chemoreceptive circumventricular organ in the medulla oblongata (63) implicated with nausea, emesis, and motion sickness. An example for a depolarization associated with a conductance decrease (block of a potassium channel) is illustrated on a neuron from the pontine reticular formation in Figure 12A.

There are strong mutual connections between the histaminergic and the other aminergic nuclei in the mid-brain and brain stem which display great similarities in morphology as well as cellular and systemic physiology. They are actually comparable to an orchestra, a self-organizing network, possibly with the orexin/hypocretin neurons acting as a director and the histaminergic neurons as the first violin.

1. Cholinergic nuclei

The cholinergic nuclei in the brain stem, the basal forebrain and the septum receive a strong histaminergic

innervation (548) and are densely covered with histamine receptors, especially of the H1 type (66). Infusion of histamine in the lateral dorsal tegmentum (a cholinergic nucleus) leads to increased vigilance accompanied by EEG desynchronization (407). Khateb and co-workers (334, 335) demonstrated a depolarization of cholinergic neurons in the pons and in the basal forebrain. Histamine infusion into this region increases ACh release in the cortex (99) and the ventral striatum (585), whereas H3 heteroreceptor activation has opposite (depressant) effects on acetylcholine release (61, 146).

Cholinergic neurons in the medial septum project to the hippocampus where they evoke theta-activity. They are excited by histamine (H1R) (213). This nucleus also contains a population of GABAergic neurons that is critically involved in the production of hippocampal theta. These neurons are excited directly by histamine (H1R and H2R) and indirectly through cholinergic neuron excitation (H1R) (828). Stimulation of the TMN also leads to ACh release in the hippocampus (482). Thus the role of the cholinergic afferents in cortical activation and wakefulness is strongly promoted and controlled by the histaminergic system (461, 462). The excitatory action of histamine on the cholinergic neurons is not counterbalanced by an excitatory cholinergic effect of comparable power and duration on histamine neurons: they respond only very briefly to fast-desensitizing nicotinic receptor activation (780, 783).

2. Locus coeruleus (norepinephrine)

The noradrenergic neurons in the locus coeruleus are excited by a postsynaptic H1R-mediated action in ~80% and by a postsynaptic H2R-mediated action in ~40% of the neurons. Single-cell RT-PCR revealed the same percentages for the expression of these receptors and an expression of the H3R in ~30% of the noradrenergic neurons (367). H3R-mediated electrophysiological actions on noradrenergic neuronal somata were not detected, but norepinephrine release from axon varicosities is reduced in brain slices from animals and humans (645, 646). As histaminergic neurons are disinhibited through a presynaptic action of norepinephrine (α 2R) (512, 707), the two systems mutually excite each other at the somatic level.

3. Raphe nuclei (serotonin)

Serotonergic neurons in the dorsal raphe are directly excited by histamine convergent with multiple other arousal systems (norepinephrine, acetylcholine, orexins/hypocretins) (83). H1-receptor activation causes an inward current through the opening of a mixed cation channel (83) likely of the TRPC family (672). Figure 12B illustrates this inward current associated with an increased channel noise indicative of channel opening. The firing of serotonergic dorsal raphe neurons can also be de-

pressed by microionophoretic histamine through H2R activation (380).

4. *Ventral tegmental area/substantia nigra (dopamine)*

Dopamine release in the striatum is under the control of H3R, suggesting the presence of H3R in dopaminergic axons (645). The substantia nigra pars reticulata receives moderate to dense histaminergic innervation (10, 124, 548) and GABAergic inhibition directly from the striatum. H3R activation reduces GABA and serotonin release (753) in this pathway (198). The GABAergic neurons are excited through H1R in both the substantia nigra and the ventral tegmentum of the rat, while the dopaminergic neurons in these structures are not directly affected (364); they are indirectly inhibited by histamine. In a study on mouse slices, both H1R and H2R were found involved in the histaminergic excitation of inhibitory projection neurons; furthermore, H3R activation inhibited these neurons (855).

5. *Periaqueductal grey*

The periaqueductal grey (PAG) is a key structure in pain control and behavioral defense responses. The PAG harbors POMC-positive neurons that release opioids and a wake-active population extending the mesolimbic dopaminergic system (636). Histamine in the PAG can evoke antinociception (506, 752), while morphine injection systemically or into the PAG increases the release and metabolism of brain histamine (48), suggesting reciprocal interactivity. H2R activation in the PAG may be involved in the control of defensive behavior following activation of neural substrates of fear (634).

6. *Nucleus of the solitary tract*

Histamine in the vagal complex of the nucleus tractus solitarius is released from a dense network of histaminergic fibers (10), and H3R likely control transmission of interoceptive, immunogenic (369), and thermogenic signals (124, 324, 853). Central histamine application or direct electrical stimulation of the TMN mediates tracheal dilation and pressor responses elicited by hyperthermia and activation of H1R in autonomic centers of the vagal complex and rostral ventrolateral medulla (323, 324).

7. *Trigeminal nucleus*

Neurons in trigeminal nuclei express H1R and H3R (386) and exhibit reciprocal excitatory relationships with histaminergic TMN neurons (154, 276, 282, 628). Mastication and feeding are potent activators of the brain histamine system (628). Oral sensations, in turn, conveyed through sensory and gustatory afferents of the trigeminal and facial nerve, respectively, provide substantial glutamatergic excitatory input to the brain promoting cortical activation and arousal. Excitatory inputs from nociceptive trigeminal nerve endings in the meninges and brain vasculature (154) play important roles in the pathophysiology of headaches (see sect. XI).

matergic excitatory input to the brain promoting cortical activation and arousal. Excitatory inputs from nociceptive trigeminal nerve endings in the meninges and brain vasculature (154) play important roles in the pathophysiology of headaches (see sect. XI).

8. *Vestibular and cochlear nuclei*

Microelectrophoretic experiments in the vestibular nuclei revealed H1R-mediated excitation and H2R-mediated inhibition of firing (639). Intracellular recordings in the medial vestibular nucleus identified several types of neurons that were depolarized by histamine through H2R activation in guinea pig brain stem slices (568, 663). In the rat, a similar excitation was found in slices of the medial vestibular nucleus, displaying both H1R and H2R components (132, 802). The vestibular reflex is modulated by histamine through both H2R and H3R at the level of the vestibular nuclei in the guinea pig (829). Interestingly, the vestibular hair cells, the source of vestibular nerve activity, are also sensitive to histamine H1R, H2R, and H3R activation (37), causing influx and intracellular release of Ca^{2+} , which is needed to release glutamate from these hair cells (760). Stimulation of the vestibular nerve causes histamine release in the brain stem and the hypothalamus (263, 264, 728, 777). Histamine receptors are found in the cochlea (37), and histamine can affect microcirculation and microphonic compound action potentials. The cochlear nuclei display histamine-immunoreactive nerve fibers (548) and activation of neurons by electrical stimulation of the lateral hypothalamus (821), but little is known on histaminergic transmission in this target.

C. Cerebellum

A moderately dense network of histamine-immunoreactive fibers is seen in the molecular and granular layers of the cerebellum in several species including human. These fibers run parallel to the Purkinje cell layer after traversing it perpendicularly (550). Purkinje cells of the cerebellar cortex as well as neurons in the nucleus interpositus all exhibit H2R-mediated excitatory responses to histamine bath perfusion in slices from rats (677). Granule cells are excited through both H1R and H2R activation (399, 754, 856). Histaminergic transmission in the cerebellum has been demonstrated by an enhanced phosphoinositide turnover following histamine methyltransferase inhibition (342, 731). An increased motor performance, balance, and coordination after histamine injection and the opposite effects after injection of an H2R antagonist in the interpositus nucleus highlight the functional importance of the histaminergic projection to the cerebellum (693).

D. Hypothalamus

Early work using histamine injections in the hypothalamus has revealed actions on feeding, drinking, and body temperature (222, 392, 424). Excitation via the H1R has been reported on most neurons investigated, but H2R-mediated inhibition has been observed on oxytocin neurons of the paraventricular nucleus (250, 839) and in the suprachiasmatic nucleus (419) (see sect. IX).

1. Preoptic area

Sleep-active neurons in the VLPO switch off TMN neurons but do not seem to be reciprocally responsive to histamine *in vitro* (191). In contrast, presumably GABAergic neurons in medial preoptic area (MPO) including warm-sensitive neurons are mostly excited by histamine through H1R activation (719, 720, 768). Through this action histamine may indirectly inhibit VLPO neurons and modulate core body temperature during sleep and fever responses (721).

2. Suprachiasmatic nucleus

The suprachiasmatic nucleus (SCN) is innervated by histaminergic fibers, and histamine application *in vitro* phase shifts the neuronal firing of SCN neurons in a manner similar to light, i.e., delaying it in the early subjective night and phase advancing it in the late subjective night (121). Histaminergic excitation of SCN neurons is mediated by H1R and NMDA receptors, inhibition by H2R (419, 699), which are highly expressed in the SCN (330). The SCN of the Syrian hamster displays few histaminergic fibers, and microinjections of histamine in this region do not mimic the effects of light on circadian rhythms, indicating that histamine does not play a prominent role in circadian rhythm regulation in this species (655). Interestingly, significant amounts of histamine can be found within SCN neurons of mice but not in mice lacking HDC (471). Moreover, HDC-KO mice show alterations in both circadian rhythms of behavior and clock genes, but mainly outside the SCN (2), suggesting important but not yet well-characterized roles of histamine in circadian rhythm and molecular clock control (see sect. IX).

3. Supraoptic nucleus and paraventricular nucleus

Histamine effects on vasopressin (AVP)-, oxytocin-, and CRH-containing neurons in the supraoptic (SON) and paraventricular nuclei (PVN) are implicated in a number of homeostatic functions. Histamine-induced secretion of ACTH, β -endorphin, α -melanocyte stimulating hormone (MSH), and prolactin is mediated via activation of AVP, oxytocin, and CRH neurons as visualized by *c-fos* expression, particularly in the context of stress (351, 355). Stress-induced hypothalamo-pituitary-adrenal axis activa-

tion and corticosterone release is modulated by histamine in a H1R-, prostaglandin-, and NO-dependent fashion and blunted when HDC is blocked by α -FMH (87, 88). Reciprocal H1R-mediated excitatory interactions between CRH and histamine neurons are also part of GLP-1 signaling pathways regulating feeding behavior (214). Histamine and stress-induced prolactin responses involve serotonergic neurons (312, 349, 350) and inhibition of the inhibiting tuberoinfundibular dopaminergic neurons by H2R (514, but see Ref. 176). Through strong innervation and excitatory effects on SON and PVN neurons, histamine also participates in the regulation of growth hormone and TRH release from neurons (352, 651; see below).

Local injections of histamine in the rat (387, 772–774), cat, and goat SON evoke antidiuresis (56). Likewise, endogenous histamine induces *c-fos* expression in both the SON and PVN (351, 790). The prime role of the histaminergic system in AVP and oxytocin release in conscious rats (357) and humans (347) has been substantiated by application of histamine, agonists and antagonists. Dehydration induces HDC gene expression and release of AVP through activation of histaminergic neurons (348). SON neurons containing the antidiuretic hormone are depolarized by histamine. This has been demonstrated not only by local application but also by stimulation of the TMN, through synaptic contact with SON neurons (248, 812, 839). Histamine increases firing rate and prolongs depolarizing afterpotentials that promote the phasic bursts (238, 239, 248, 402, 689) underlying pulsatile AVP release from axonal endings in the neurohypophysis (30, 689). The H1R-mediated excitation of SON has been attributed to several mechanisms: block of a K^+ conductance (248, 603), intracellular IP_3 -mediated Ca^{2+} release, activation of a Ca^{2+} -dependent cationic current, and a NCX (248, 402, 689). Single TMN stimuli elicit EPSPs in vasopressinergic SON neurons, while prolonged stimulation blocks non-NMDAR-dependent excitatory synaptic currents (401) and results in a marked H1R-dependent increase of inter-neuronal coupling mediated through NO and cGMP signaling cascades (249, 841). SON oxytocin neurons respond to TMN stimulation with fast chloride-dependent IPSPs mediated by a presumed ionotropic receptor that is sensitive to H2R antagonists. Furthermore, a reduction of gap junctional coupling and a prolonged decrease of excitability are metabotropic, H2R, and cAMP-dependent effects (250, 839). The coupling between these neuroendocrine cells probably plays an important role in synchronizing their action during pulsatile release of vasopressin and oxytocin.

Activation of histamine neurons by thioperamide, an H3R antagonist, enhances *c-fos* mRNA expression and Fos-like immunoreactivity in magnocellular neurons of rat supraoptic and paraventricular nuclei through H1R activation (790). Suckling increases histamine and oxytocin concentrations in the PVN through H1R and H2R

activation. Histaminergic activity is also necessary for oxytocin release during parturition and lactation (53, 248). H2R activation inhibits oxytocin neurons possibly to suppress untimely release of oxytocin, and this effect is overcome by the H1R-mediated excitation during parturition (434).

4. Arcuate nucleus and ventro/dorsomedial hypothalamus

The arcuate nucleus (ARC) integrates nutritional-metabolic signals and controls long-term energy uptake and metabolism. Neurons in the ventromedial (VMH) and dorsomedial (DMH) hypothalamus receive input from both the ARC and SCN, and interact with histaminergic and hypocretinergic neurons to form a network that acts as an entrainable oscillator controlling neuroendocrine and feeding rhythms (25, 472). Histamine through H1R conveys signals for suppression of food intake to the satiety center in the VMH (and the PVN) (535, 628). Feeding rhythms are disturbed in H1R-deficient mice (453), and H1R antihistamines given in the ventricles induce feeding and suppress the firing of glucose-sensitive neurons (186) selectively in the VMH but not other regions. Early ionophoretic studies reported a H1R-mediated excitation and H2R-mediated depression of firing (230, 607). An H1R-mediated excitation was also found in neurons in the ARC responsive to substance P (772). This likely influences anterior pituitary output, since histamine and substance P have similar effects on LH and prolactin secretion (313). Neurons in the VMH contain the liberating or inhibiting hormones that reach the hypophysis through a local portal vascular system in the hypophyseal stalk and regulate the hormone release from the hypophysis: the peptides growth hormone releasing hormone (GHRH), prolactin releasing hormone (PRH), vasoactive intestinal polypeptide (VIP), thyrotropin releasing hormone (TRH), GnRH, and dopamine (prolactin inhibiting hormone, PIH). The histaminergic neurons densely innervate these regions and participate in the regulation of pituitary hormone secretion through both H1R and H2R (320, 355, 769). Release of the anabolic hormones GH and TSH is inhibited through exogenous (intracerebroventricular) and endogenous histamine, presumably through an action on TRH- and GHRH-containing neurons at hypothalamic levels (513). Lesions of the histaminergic tract abolished this effect (225, 770).

5. Lateral hypothalamic and perifornical areas

The lateral hypothalamus and perifornical area contain peptidergic neurons expressing orexin/hypocretin (Hcr) and melanin-concentrating hormone (MCH). Hypocretin neurons (136, 820) activate the aminergic wake-promoting nuclei (83, 163, 366, 661) and are crucial for behavioral state bistability (636). Dysfunction is causally

related to the sleep disorder narcolepsy (473, 680). Although there is a strong mutual innervation and functional interaction between hypocretin neurons and the TMN (415), direct electrophysiological effects in vitro have only been observed in one direction so far: hypocretins excite histaminergic neurons (163), but histamine does not seem to affect the excitability of hypocretin neurons (400). Preliminary data suggest that histamine excites MCH neurons in vitro (51).

E. Thalamus

A correlation between histamine innervation and receptor expression in human brain suggested mediation of tactile and proprioceptive thalamocortical functions through multiple receptors (304). The relay neurons in the lateral geniculate nucleus (LGN) are gatekeepers of cortical activation, arousal, and consciousness. When firing in a bursting mode at membrane potentials around -60 mV, no sensory information can pass to the cortex, at a slightly more depolarized level however, they fire continuously and the gate is open (462). Among other transmitters, this depolarization is promoted by histamine through combined activation of both H1R and H2Rs (462), which blocks a potassium current and enhances a hyperpolarization-dependent cation current I_h (HCN2) (Fig. 15). Furthermore, GABAergic perigeniculate neurons are inhibited by histamine opening chloride channels, presumably an ionotropic action on an H2-like receptor (390). Increased activity of the histaminergic system could in this way dampen thalamic oscillations during sleep-waking transition. Inhibitory actions of histamine ionophoresis to intralaminar thalamic neurons have also been reported (686). Visual responses of neurons as well as basal activity in the dorsolateral geniculate nucleus are enhanced by stimulation of the histaminergic nucleus in the cat (776).

F. Basal Ganglia

High densities of H2R and H3R are found in the basal ganglia (123, 448, 573, 764, 792), especially on the principal neurons of the striatum, the GABAergic medium spiny neurons (MSN) (212, 580, 622), but the innervation is relatively weak. H3R mRNAs in the cortex and in the substantia nigra pars compacta indicate the presence of H3 heteroreceptors on the major inputs to the striatum. No such signal is found in the ventral tegmental area (573). In addition to neuronal sources, biochemical experiments have indicated histamine actions derived from neurolipomastocytoid cells (type II mast cells) in the neostriatum (122, 621). Microelectrophoretic experiments revealed excitatory actions of histamine on presumably MSN in anesthetized rats (686). In contrast, H3R activation inhibits glutamate release from rat striatal synapto-

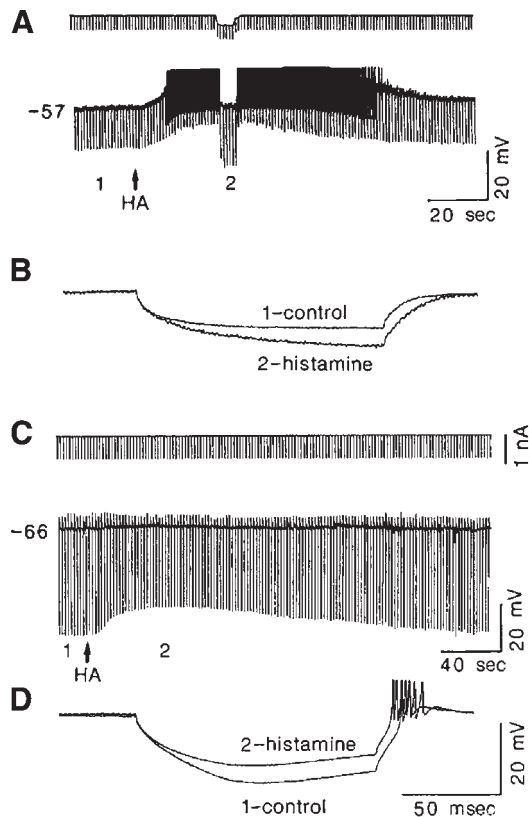


FIG. 15. Histamine actions in thalamic relay neurons (slices from lateral geniculate nucleus). A: histamine causes an H1R-mediated depolarization. Manual clamp (2 in A and B) reveals an apparent conductance decrease (block of a leak current). C: small H2R-mediated depolarization associated with a substantial increase in apparent membrane conductance at hyperpolarized membrane potentials. [Modified from McCormick and Williamson (462).]

somes (485). Indeed, no histamine effects on membrane potentials or conductances were seen in intracellular recordings from MSN in slices, but a significant H3R-mediated reduction of glutamatergic transmission and synaptic plasticity evoked by cortical stimulation was observed (146). This action is severely compromised in an animal model of hepatic encephalopathy along with abnormalities of basal ganglia output function and behavior (674). The dopaminergic nigrostriatal input that controls glutamatergic excitation (and drive of MSN) is regulated by histamine H3 heteroreceptors (645).

Giant, presumably cholinergic, interneurons isolated from the striatum are excited through a combined action of H1R and H2R blocking a leak potassium conductance (499) in keeping with histaminergic modulation of acetylcholine release in the striatum by these (591) and H3R (590). Bell et al. (55) find H1R exclusively responsible for the excitation of identified cholinergic interneurons. Single-cell RT-PCR revealed only H1R- but not H2R mRNA in these neurons. The vast majority of neurons in the globus pallidus (104) and in the nucleus ruber (105) are excited by H2R activation in rat brain slice preparations.

Field potentials in the nucleus accumbens evoked by stimulation of the fimbria, which connects the hippocampus with subcortical structures, are reduced by histamine in anaesthetized rabbits, apparently via a stimulation of GABAergic interneurons through H2R (113). Local injection of histamine directly in the nucleus accumbens causes a transient H3R-mediated suppression of locomotion followed by an H1R-mediated hyperactivity (76). This histamine-induced hyperactivity can be increased by chronic intra-accumbens administration of a TRH analog (77) and suggests cooperativity of histamine and TRH in behavioral arousal control.

G. Amygdala

Electrophysiological evidence for histamine effects in the amygdala is scarce compared with anatomical and functional data, indicating prominent histaminergic innervation (548), receptor expression, and turnover (293), and modulation of amygdala-dependent innate and learned fear, reinforcement of memory (22, 44, 60, 86, 92, 558, 614), and epileptic kindling (319, 763) (see sect. XI). Intracellular and field potential recordings in rat brain slices (301) revealed that histamine, via presynaptic H3R and a currently unknown mechanism, has bidirectional effects (depression and potentiation, respectively) on excitatory synaptic transmission in the basolateral amygdala. Mice deficient in ApoE, a lipoprotein receptor associated with development and regeneration, display reduced histamine levels and H3R antagonist-induced histamine release selectively in the amygdala (785).

H. Hippocampus

Two histaminergic fiber bundles reach the hippocampus, through the fornix and a caudal route. The innervation appears not very dense, but histamine actions are quite strong on this structure and have been studied in much detail in rat brain slices. The input pathway to the dentate gyrus from the entorhinal cortex is suppressed by H3R activation in vitro (81, 82) and in vivo (445). Stimulation of the TMN during exploratory behavior also inhibits its transmission here (807), and this effect is blocked by intracerebroventricular injection of an H3R antagonist.

The glutamatergic synapses on pyramidal neurons are not directly affected at the presynaptic level as the EPSPs are unchanged by histamine. Nevertheless, a striking and long-lasting enhancement of synaptically evoked population spikes generated by synchronously activated pyramidal neurons in CA1 and CA3 is observed under histamine. A postsynaptic effect at H2R in the CA3 region causes a strong increase in the response to glutamate released at the mossy fiber synapse (657, 843). CA3 pyramidal cells have an endogenous tendency to synchronize

and discharge bursts, a pattern that superimposes as sharp waves in the EEG. In rat brain slices, burst firing can be evoked by afferent stimulation while in slices from the mouse hippocampus bursts occur spontaneously and are massively facilitated by H2R activation (843). This is an important effect in the light of the decisive role of CA3 synchronization in synaptic plasticity and the formation of memory traces (90) (Fig. 16).

CA1 pyramidal cells and dentate granule cells are directly excited by postsynaptic H2R activation (223, 233, 234). Firing rates and population spikes are potentiated (80, 659). Intracellular recordings revealed mostly a depolarization caused through a shift in the activation of the I_h current (563). Furthermore, H2R activation blocks the Ca^{2+} -dependent K^+ channel responsible for a slow and long-lasting afterhyperpolarization (sAHP) and the accommodation of firing in response to depolarizing stimuli (233, 234) (Fig. 17). This effect is also seen in hippocampal pyramidal cells after stimulation of the histaminergic neurons in organotypic cocultures of posterior hypothalamus and hippocampus (141). Thus, even in the absence of a depolarization, the response to a given excitatory stimulus in a neuron residing in quiet readiness can be much potentiated by histamine. Other amines that are positively coupled to adenylyl cyclase produce similar actions: serotonin, through 5-HT_2 , norepinephrine through β -receptors, and dopamine through D1 receptors. Dopamine at low concentration has the opposite effect; it enhances the afterhyperpolarization and the accommodation of firing (234) probably

through D2R and negative coupling to adenylyl cyclase. In keeping with this, other neuroactive substances using this signaling pathway like the endogenous antiepileptic and sleep pressure factor adenosine (237) (A1R) and GABA (B-receptor) exert such an action (204). Ca^{2+} -dependent K^+ channels are a common effector pathway for cAMP-PKA signaling through many neuromodulators and provide an important point of convergence for regulation of neuronal excitability and specifically hippocampal physiology (562). The exact molecular structure of the apamin-insensitive Ca^{2+} -dependent potassium channel(s) underlying the sAHP is still unknown (709).

The pharmacological signature and duration of histamine effects on PKA signaling, ion channel function, and neuronal excitability can be monitored under conditions of synaptic isolation (low Ca^{2+} , high Mg^{2+}) (659). Here, histamine exerts biphasic and bidirectional effects on pyramidal cell firing in the CA1 region, an initial and short-lasting depression mimicked by the H1R agonist 2-fluorophenylhistamine followed by a long-lasting (>2 h) excitation mimicked by the H2R agonist impromidine. The magnitude and duration of the excitation is much less effective than a coincident activation of both, H1R and H2R. Thus histamine triggers a signaling cross-talk through $G_{q/11}$ -coupled short-lasting H1R-mediated and IP_3 -dependent surges of intracellular Ca^{2+} (255, 805), $G_s\alpha$ -coupled H2R-mediated cAMP/PKA, and coincident NMDAR activation providing long-term control over neuronal excitability in the hippocampus (659).

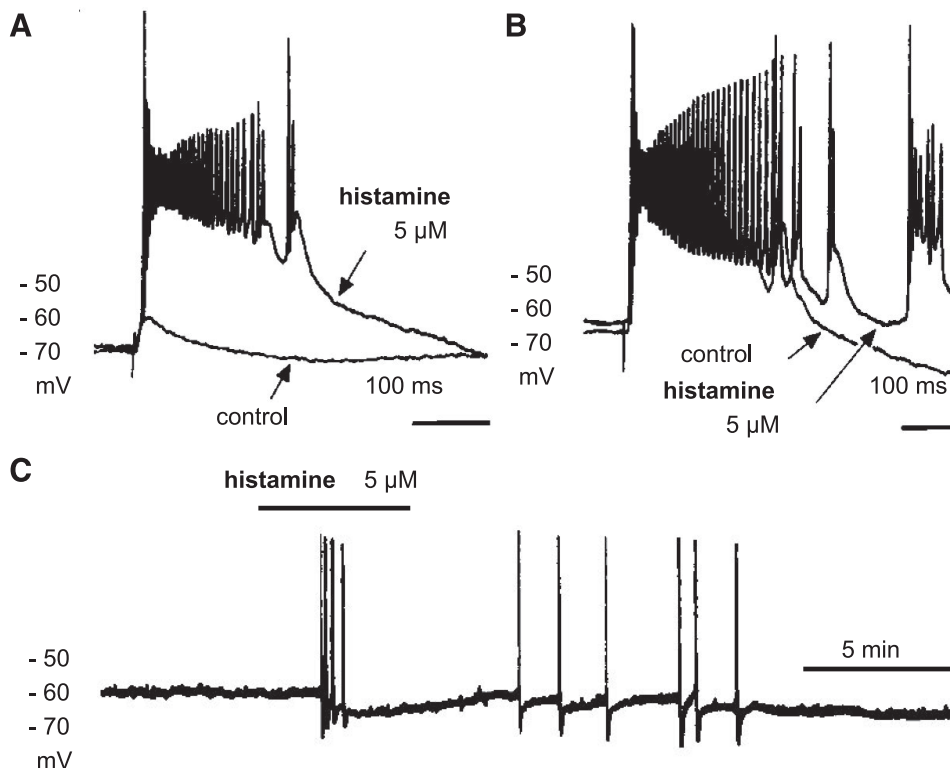


FIG. 16. Effect of histamine in the hippocampal CA3 region. Histamine increases burst activity in pyramidal neuron. *A* and *B*: in response to synaptic activation. *B*: bursts are prolonged under histamine [H2R-mediated block of g_K (Ca^{2+})]. *C*: induction of bursting in a silent pyramidal cell at longer time scale; each vertical excursion represents a full-blown burst such as shown in *A* and *B*. [Modified from Yanovsky et al. (843).]

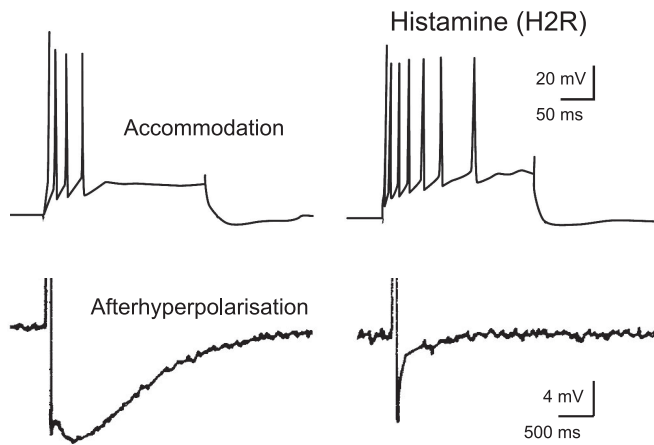


FIG. 17. Histamine actions through H2R and cAMP in hippocampus. Block of the accommodation of firing (human CA1 pyramidal cell in a slice preparation) and the long-lasting afterhyperpolarization (dentate granule cell). A Ca^{2+} -dependent K^+ current (small K) is responsible for these phenomena. [Modified from Haas and Panula (235).]

In spite of the aforementioned strong excitatory and potentiating effects on principal cells and synaptic transmission *in vitro*, histamine actions on the hippocampal function *in vivo* and on the whole are inhibitory and anticonvulsant. Interruption of histaminergic afferents leads to an overexcitable hippocampus (unpublished observations), and H1R antihistamines are epileptogenic (847). Loss of direct (H1R-mediated) inhibitory actions on pyramidal cells and the reduction of excitatory drive in dentate granule cells may account for the proconvulsant effects of antihistamines, but even more likely anticonvulsant are strong excitatory actions of histamine on inhibitory interneurons. This is evident from the regularly seen massive increase in the frequency of spontaneous GABAergic potentials in pyramidal and dentate granule cells (223, 233). Extracellular recordings from electrophysiologically identified alveus/oriens interneurons also revealed such an H2R-mediated excitation (843) (Fig. 18). In patch-clamp recordings from these interneurons, the excitation was not observed presumably due to the cell dialysis. However, in these recording conditions, another interesting action was observed: the maximum firing rate of the interneurons was curtailed by H2R-mediated phosphorylation of an identified K^+ channel, Kv3.2, providing a pathway for the regulation of high-frequency oscillations in the hippocampus (35). Intracerebroventricular-injected pyrilamine (H1R antihistamine) increases the occurrence of sharp wave-related ripples in freely moving rats (358), while intraperitoneal injection of zolantidine, an H2R antagonist that reaches the brain, reduces the occurrence of these high-frequency oscillations (581), which are involved in memory trace formation (90). GABAergic and cholinergic neurons in the septum that project to the hippocampus are also directly excited by histamine (213, 828).

I. Cortex

In the 1970s, single-unit recordings and ionophoretic local application of substances revealed histamine-sensitive neurons and functional histaminergic projections to the cortex (238, 638). Depressant actions of histamine but not those of GABA were blocked by the H2R antagonist metiamide (232, 240, 572, 638). The blocker of ligand-gated chloride channels, picrotoxin, blocked H2R-mediated depressions of firing (572). Thus excitation of interneurons by histamine or histamine-gated chloride channels (250, 390) may be responsible. Such channels are prominent in molluscs and arthropods (see sect. v). Excitations were less frequently seen in response to histamine ionophoresis, the probability to pick up the small interneurons was small with the multibarreled electrodes used in these experiments.

Intracellular recordings from human cortex revealed clear H2R-mediated excitatory actions through block of $\text{gK}^+(\text{Ca}^{2+})$ (461, 462), as described in the hippocampus of several species including human (234, 562). Furthermore, H1R-mediated excitation of principal cortical neurons has been identified as the target of the sedative antihistamines (603) and is in line with PET studies in the human cortex and thalamus (723). A perforated patch-clamp study in olfactory bulb slices from newborn rabbits has revealed outward and inward currents in interneurons through H1R and H2R, respectively, while no effects were observed in the principal mitral cells (299). Both these currents reversed at the potassium equilibrium. Histamine-sensitive GABAergic interneurons in the olfactory bulb represent a cell population that is continuously replaced by adult stem cells throughout life (421).

J. Synaptic Plasticity

Long-term potentiation (LTP) and long-term depression (LTD), persistent increases or decreases in the effi-

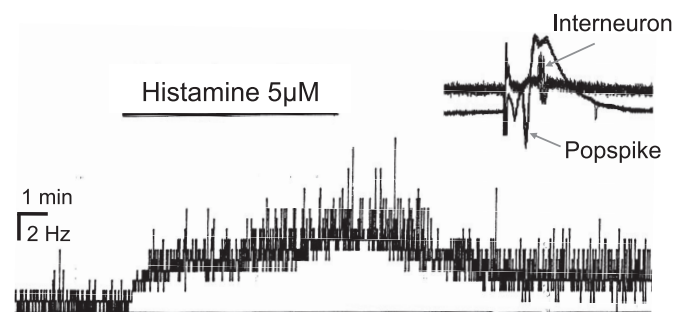


FIG. 18. Excitation of interneuron in the oriens/alveus region by histamine. Extracellular recording from electrophysiologically identified interneuron that fires at an almost fixed latency after the population spike in response to Schaffer-collateral stimulation (see *inset*); rate meter record is below.

cacy of excitatory synaptic transmission, are cellular correlates of memory trace formation. Many forms of this synaptic plasticity involve the activation of NMDA receptors, an intracellular surge of Ca^{2+} , and activation of plasticity-related protein kinases such as calmodulin kinase II, PKC, and PKA; the latter can also evoke NMDAR-independent LTP. The voltage-dependent block by Mg^{2+} confers a coincidence detection mechanism to NMDA receptors. A reduction of this block through H1 receptors and PKC facilitates NMDA receptor activation (561). Two further mechanisms promote synaptic plasticity through H1 receptor signaling: the release of Ca^{2+} from the endoplasmic reticulum by IP_3 and the synergism with H2 receptor-coupled cAMP/PKA cascades (255, 659). The latter can by itself evoke (368, 659) and promote LTP (80, 84). A brief perfusion of a hippocampal slice with histamine results in a LTP without any high-frequency stimulation. The helper action of H1R is evident by the much stronger effect of histamine on LTP of excitability compared with impromidine, a selective and highly potent H2R agonist (659) (Fig. 19).

Histamine also exerts a direct potentiating action on NMDA receptors through their polyamine binding site (54, 798) (Fig. 14). We should remember here the reason for the late recognition and long neglect of the brain histamine system due to the cross-reaction with the polyamines spermine and spermidine that prevented its histological documentation by early histochemical methods

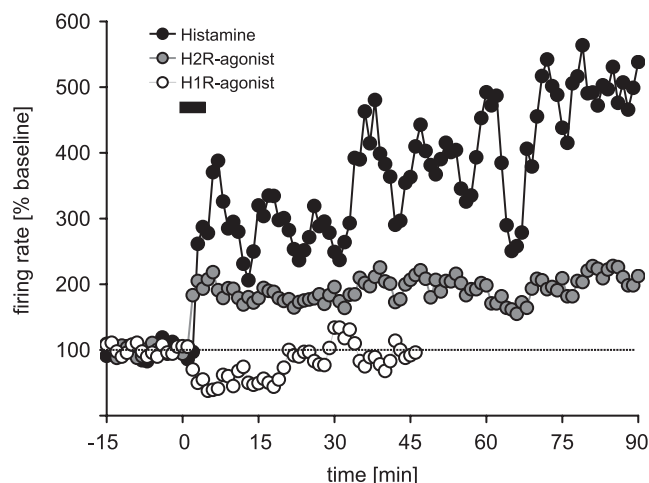


FIG. 19. Histamine induces long-term potentiation (LTP) of cell firing in the hippocampus. Shown are pooled averaged data illustrating long-lasting effects of brief application (black bar) of histamine (1–10 μM , $n = 7$), of the specific and highly potent H2R agonist impromidine (0.3–3 μM , $n = 11$), and of the H1R agonist 2-(3-fluoro)-phenylhistamine (1–50 μM , $n = 9$) on hippocampal pyramidal cell firing in the CA1 region in low- Ca^{2+} /high- Mg^{2+} solution (synaptic isolation). Standard errors are omitted for clarity. Similar histamine effects can be observed on amplitude of population spikes evoked by synaptic stimulation. Note the opposing effects of H1R (depression) and H2R (potentiation) activation, and synergism by receptor coactivation through histamine. [Modified from Selbach et al. (659).]

(218). The NMDA current potentiation is coupled to the NR1/NR2B receptor type (818) and is exquisitely sensitive to pH (641, 844), indicating an action antagonistic to the known NMDA receptor depression by protons. It is thus more pronounced during acidic shifts in tissue pH that occur during metabolic challenges such as intense neuronal firing, e.g., during burst activity evoking synaptic plasticity or under pathological conditions such as hypoglycemia, ischemia, or epilepsy. Thus the histaminergic system can detect changes in tissue pH with consequences for synaptic plasticity, whole brain physiology, and pathophysiology. A central role for such pH sensing has recently been attributed to the neighboring and functionally related orexin/hypocretin neurons too (819).

The H2R-mediated block of Ca^{2+} -dependent K^{+} channels increases the number of action potentials fired by a given stimulus and facilitates further Ca^{2+} inflow. Thus the synchronous burst discharges of selected pyramidal cell populations in the CA3 region that appear as sharp waves in field recordings are robustly potentiated by histamine (842, 843) (Fig. 16). These discharges represent a natural trigger for LTP (91, 660) and play a decisive role in memory trace formation (90). The H3 receptor-mediated reduction of glutamatergic transmission in the dentate gyrus and in the corticostriatal pathway lasts up to several hours; this long-term depression is much more prominent in rats than in mice (81, 82, 146, 445). In rats carrying a portacaval shunt, a model for liver disease and hepatic encephalopathy, this form of synaptic plasticity is absent (674).

Thus molecular and mechanistic signatures of histamine actions in the hippocampus suggest that it might play a role in protein synthesis-dependent enduring forms of long-term synaptic plasticity such as late phases of LTP and/or LTD (610). These forms of synaptic plasticity, like memory consolidation, require coactivation of plasticity-related protein kinases including PKC and PKA, and protein synthesis, all of which can be brought about by histamine through coincident activation of H1R, H2R, and NMDAR. Furthermore, trafficking of distinct AMPA-GluR subunits plays a key role in LTP and is influenced by histamine in a Ras-PI3K-PKB- and state-dependent manner (600). All this suggests a convergence in the signaling pathways underlying both nutritional-metabolic and behavioral state-dependent control of long-term synaptic plasticity and memory. Histamine deficiency improves consolidation of contextual fear corresponding with improved LTP in the CA1 region before and decreased LTP after conditioning (420). Hippocampal LTP is reduced in H1R-KO and H2R-KO mice (127).

K. Glia and Blood-Brain Barrier

Glia cells express H1R and H2R to varying degrees. H1R mediated IP_3 signaling increases intracellular Ca^{2+} ,

often biphasic and in form of oscillations in astrocyte processes (280, 316). Confocal imaging revealed, apart from the cytosolic, a mitochondrial source of histamine-evoked Ca^{2+} oscillations (315). Astrocytes can release glutamate in response to neuronally released transmitters, including histamine through H1R activation (676). Histamine promotes release of neurotrophins and cytokines from astrocytes in cultures (317) and ATP in hypothalamic slices (670). Histamine effects on glia may play a role in brain energy metabolism, glycogenolysis, electrolyte balance, transmitter clearance, and BBB permeability (439, 749). Inflammatory processes caused by histamine infusion involving microglia in the striatum lead to dopaminergic degeneration (791). Histamine causes BBB opening (644), and studies of pial vessels and cultured endothelium revealed increased permeability mediated by H2R, elevation of $[\text{Ca}^{2+}]_i$, and an H1R-mediated reduction in permeability (1). HDC, H1R, and H2R are expressed in neuroepithelial tissue during development (328), and glial elements in the ependym of HDC-KO mice are strongly activated by acute stress (541). This suggests that the cerebrospinal fluid is part of histaminergic signaling in the developing and challenged brain (328, 330, 339). Strategically positioned to interact with the cerebrospinal fluid, histaminergic TMN neurons may sense and provide guidance cues for migration of neuronal and glial progenitors to their final destination along the flow of the cerebrospinal fluid.

In view of the important effects of histamine on vascular permeability in peripheral vessels, a similar function in the cerebral vasculature was investigated by Joo et al. (308). They found an enhanced pinocytosis of endothelial cells and an edematous swelling of the astrocytic end-feet system (151) as a result of H2R and adenylyl cyclase activation (331). Histamine also enhanced the penetration of serum albumin into the capillaries. Endothelial cells do not synthesize histamine or histamine receptors, but they can take up histamine in the cytoplasm and the nucleus (329).

IX. HOMEOSTATIC BRAIN FUNCTIONS

Pharmacological studies in intact and histamine-deficient animals as well as humans link brain histamine with homeostatic brain functions and neuroendocrine control. The impact of histamine on neuroendocrine control is well documented. Brain histamine is deeply concerned with the control of behavioral state, biological rhythms, body weight, energy metabolism, thermoregulation, fluid balance, stress, and reproduction (267, 651, 799).

TMN neurons arborize extensively in the hypothalamus and influence the release and function of several hypothalamic peptides and hormones (309, 356, 389, 453,

540, 651) (Fig. 11). Histamine stimulates the secretion of ACTH, β -endorphin (mediated by CRH and AVP), α -MSH (mediated by catecholamines), and PRL (mediated by dopamine, serotonin, and AVP) and participates in the stress-induced release of these hormones. Histamine is also implicated in estrogen-induced LH surges in females (mediated by GnRH) and suckling-induced PRL release. Histamine has predominantly inhibitory effects on the release of GH and TSH but is a potent stimulus for AVP and oxytocin release through effects in the supraoptic and paraventricular nuclei of the hypothalamus.

A. Behavioral State

Von Economo (794) described lesions in the posterior hypothalamus in victims of the influenza epidemic at the end of the First World War, who had suffered from hypersomnia "encephalitis lethargica." The brains of another cohort of patients who had suffered from insomnia displayed lesions in the anterior hypothalamus/preoptic area (794). It is likely that the hypersomnia group had been deprived of the histaminergic and the hypocretinergic neurons while the insomnia group had lost the GABAergic neurons that inhibit these waking centers during sleep. Lesion studies in rats confirmed this location of the sleep-waking centers in the rat (510). A transient inactivation of these regions was achieved by localized injections of muscimol, a long-acting GABA_A agonist. Injections in the anterior hypothalamus evoke waking and hyperactivity in cats, while injection in the rostral and middle parts of the posterior hypothalamus (the location of the histaminergic nucleus) produce a pronounced increase in slow-wave sleep (SWS) (406, 410).

The midbrain reticular formation is the source of the ascending reticular activating system (ARAS) of Moruzzi and Magoun (1949) that activates the unspecific intralaminar thalamic nuclei (497). In contrast to the aminergic afferents, this system is not essential for maintenance of cortical activation (147). A *cerveau isolé* preparation in the cat revealed that the ascending histaminergic projections control cortical activity independent of the brain stem (406). Histamine maintains wakefulness through direct projections of the TM nucleus to the thalamus and the cortex, and indirectly through activation of other ascending arousal systems, mainly cholinergic (334, 335, 828) and aminergic nuclei (83, 364, 367; for review, see Ref. 60, 235, 406). Cholinergic neurons in the pedunculopontine nucleus, basal forebrain, and septum that project to the thalamus, hippocampus, and the cortex, respectively, receive excitatory histaminergic input (334, 335, 828). The relay neurons in the lateral geniculate nucleus are depolarized and shifted to the regular firing mode which allows sensory information to pass the door into perception and consciousness. At a more hyperpolarized

state, the relay neurons produce rhythmic bursts coincident with delta waves in the EEG during sleep. The early claim for histamine as a waking substance came from the mostly unwanted sedative effects of H1 antihistamines, which readily pass the BBB. H1R antagonists cause an increase in cortical slow waves that is indistinguishable by power spectral analysis from that seen during SWS (406, 410). Some H1 antihistamines have been designed to avoid passing the BBB and lack sedation (742, 743; for review, see Ref. 836). H1R activation seems to be of general importance for the waking actions of histamine as well as other mediators promoting arousal such as orexins/hypocretins (163, 272, 415).

H3-receptor activation reduces and H3-receptor block increases histaminergic neuron activity; the former evokes sleep, the latter wakefulness in cats (403) and rodents (491, 555). In H1R-KO mice, the sleep-waking pattern shows subtle changes, and the waking response to H3R antagonists, which relieve the autoinhibition of histamine release, is abolished (271, 409). Selective block of the H2R by zolantidine, a BBB penetrating antagonist, does not seem to affect the sleep-wake cycle (492), but intracerebroventricular ranitidine increases SWS in the cat (407, 411; for review, see Ref. 406). Ciproxyfan, a specific H3R antagonist, induces waking in both H2R-KO and WT mice (555). The long-lasting potentiating effect of H2R activation on excitability of cortical neurons (234, 659) likely participates in this function, at least as far as it concerns the maintenance of vigilance and attention. Injection of the suicide substrate for HDC, α -fluoromethyl-histidine, markedly reduces histamine levels, decreases waking, and increases SWS with no changes in REM sleep in the cat (410) and rodents (343, 490, 556).

Histaminergic neurons fire during wakefulness but not during sleep, including REM sleep in cat (406, 410, 412, 413, 786), dog (305), and rodents (724) (for review, see Ref. 680) (Fig. 20). They cease firing during drowsy states before sleep and resume activity only at a high level of vigilance after wake-up (724). Similar firing patterns have also been recorded in the TMN and adjacent areas of freely moving rats (702).

Orr and Quay (1975) have shown an increased histamine release and turnover during the activity period (darkness) of rats (537), and the daily cycle of histamine release has been measured by microdialysis in freely moving animals (483). In monkeys, the histamine level correlates with individual waking periods (534).

Microdialysis experiments have shown that the extracellular histamine level is positively correlated with the amount of wakefulness in rats, cats, and monkeys. However, this has been demonstrated only in the hypothalamus (710) and the in the frontal cortex (114). Indeed, extracellular histamine shows detectable levels also during sleep. It is unknown whether HA levels follow the same pattern throughout the brain during changes in

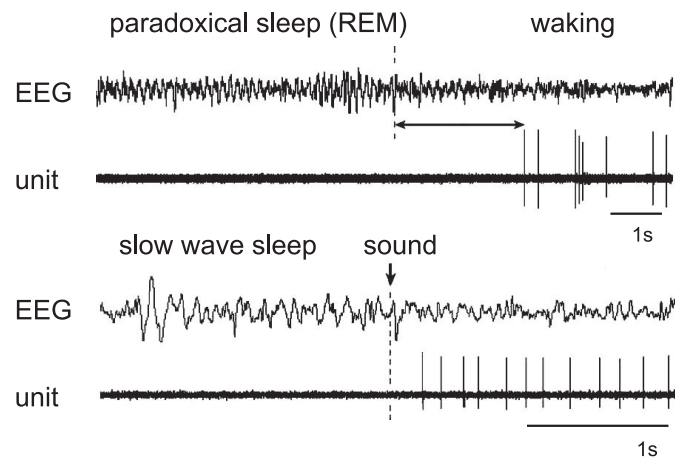


FIG. 20. Histaminergic neuron and behavioral state. Transition from paradoxical (REM) sleep (*top traces*) and slow-wave sleep (*bottom traces*) to waking in the head-restrained mouse. EEG and single tuberomammillary histaminergic neuron action potentials are shown. Waking from REM was spontaneous and was sound evoked from slow-wave sleep. [Modified from Takahashi et al. (724).]

sleep/wakefulness, or if, instead, HA levels are subject to site-specific regulation by, for example, presynaptic modulation of HA release and/or reuptake.

Furthermore, a number of investigations have shown *c-fos* activation of the TMN during waking (406, 511, 512, 642, 678, 786). The exclusive firing of TMN during waking is in contrast to the activity in REM-ON cholinergic nuclei. During cataplexy, a cardinal symptom of narcolepsy, muscle tone is lost but not consciousness (433, 680). Noradrenergic and serotonergic neurons in the locus coeruleus and the dorsal raphe cease firing under this condition while histamine neurons continue to discharge (305). During sleep paralysis, a related symptom, hypnagogic hallucinations appear as dreams in a state of consciousness.

B. Biological Rhythms

Histaminergic activity shows a clear circadian rhythm with high levels during the active period in various species including fish (89), rodents (at night), monkeys, and humans (during the day) and low levels during the sleep period. Diurnal TMN neuron pacemaker activity (235, 724) and histamine release (89, 483) as well as histamine-dependent behaviors (145, 453, 627) suggest a role of histamine in circadian rhythm. Histamine affects circadian motor activity (432, 655, 775) and feeding behaviors (285, 470, 784), and phase shifts the rodent circadian pacemaker in vitro (121, 469, 699). However, experimental evidence (2, 471, 655) corroborates early suggestions of histamine as a final transmitter entraining molecular clockworks in the suprachiasmatic nucleus (SCN) (297), the master clock of circadian rhythm in mammals (see sect. VIII D).

Recent studies in HDC- and H1R-KO mice indicate a key role for histamine in entraining molecular clockworks outside the SCN (2, 453). HDC-KO mice display lower overall activity levels (wheel-running and spontaneous locomotion) under natural light conditions and a longer free-running period under constant darkness compared with the wild type. Circadian rhythms of the clock genes *mPer1* and *mPer2* mRNA in the striatum and cortex but not SCN are significantly disrupted in HDC-KO mice (2) and H1R-KO suffer from disrupted circadian feeding rhythms (453). This phenotype is similar to mice deficient in orexin/hypocretin (25, 472) and functionally linked to a recently identified food-entrainable oscillator in the DMH (25, 472). The DMH conveys circadian-photoc and nutritional-metabolic influences from the SCN and ARC, respectively, and is crucial for a wide range of behavioral circadian rhythms (110). Efferent targets (command neurons) in the LH and PVN control neuroendocrine and sympathetic outflow, which is the major reset button for molecular clocks in the periphery (e.g., the liver). This emphasizes the convergence of circadian, histamine, and hypocretin systems (163, 271, 272, 415, 453) in synchronizing neural activities and molecular clockworks throughout and even outside the entire neuraxis (661). Data from our own lab on mice deficient in histamine, hypocretins, and *Per1* support an intriguing role of histamine, hypocretins, and clock genes in the consolidation of hippocampal long-term synaptic plasticity and memory (662).

Histamine may also play a role in infradian and seasonal rhythms, including reproductive cycles (see below) and hibernation (see above). Melatonin, a 5-HT metabolite released from the pineal gland (486), shifts circadian rhythms and resets molecular clocks at night (when histamine levels are low). It has sleep-propensating properties and is used to relieve insomnia accompanying jet lag. Melatonin receptors, which are implicated in reproductive cycles and seasonal rhythms, are also expressed in the TMN (827), but evidence for direct interactions of histamine with the melatonin or pineal timing system is limited (196, 474, 524).

C. Thermoregulation

The brain histamine system controls thermogenesis, through direct influences on key neuroendocrine signaling pathways regulating energy metabolism and nonexercise activity thermogenesis (NEAT), the most variable component of energy expenditure, and indirectly through control of behavioral activity, including feeding and motor activity (453, 495, 628). The central warm receptor is located in the medial preoptic area while the detection of “cold” relies on peripheral receptors. The body’s autonomic responses that regulate heat conservation and pro-

duction in mammals are controlled by the PVN and DMH, and the nucleus raphe pallidus, respectively. Inhibitory inputs from neurons in the MPO, responsive to temperature, may act as a hypothalamic thermostat (155). Finally, efferent pathways from the sympathetic command neurons in the PVN and LHA (371, 531) through preganglionic neurons in the spinal cord promote thermogenesis in brown adipose tissue by control of uncoupling protein expression. Both core body temperature and brain histaminergic activity exhibit circadian rhythmicity (463, 483). Moreover, most if not all of the aforementioned structures implicated in thermoregulation are targets of histaminergic innervation and modulation (453). Activation of H1Rs in the anterior hypothalamus/preoptic area may lower the set point of the hypothalamic thermostat, whereas H2Rs in the posterior hypothalamus seem to be involved in the loss of body heat (115, 221, 768). Central administration of histamine in freely moving animals causes hypothermia or biphasic responses, hypo- followed by hyperthermia (115, 116, 221). Hyperthermia, in turn, facilitates neuronal histamine release promoting tracheal dilation, polypnea, and pressor responses (295, 324). Feedback and feed-forward mechanisms may thus limit and promote, respectively, febrile responses and fever during systemic infections (108, 517) or cimetidine treatment (155, 521) (see below). Thermogenic effects of hypocretins (487, 845) and TRH (679) also rely on central histamine actions (163, 215, 845). Moreover, histamine controls clock neurons (244) and temperature preference (261) in invertebrates, suggesting an evolutionary conserved link between histamine, circadian rhythms, and temperature control.

1. Hibernation

During hibernation, metabolic functions, movement, and brain activity are reduced to a minimum for life maintenance. Histamine levels and turnover are elevated in hibernating ground squirrels in contrast to other transmitter systems (546, 629), independent from changes in HDC expression levels as revealed by genomic profiling (525). Moreover, hibernating animals display a higher density of histaminergic fibers and brain region specific alteration in histamine receptor expression profiles than euthermic animals, particularly in the hippocampus, SCN, and basal ganglia (630–632). Injection of histamine into the hippocampus delays arousal from hibernation. Hibernation in turn increases the sensitivity of hippocampal circuitries to undergo histamine-induced synaptic plasticity (519). This supports an intriguing link between the TMN histamine neurons, the hippocampus, and the master clock in the SCN, which conveys circadian-photoc influences. TRH, which suppresses food intake (215) but promotes thermogenesis (679), acts through the brain histamine system and protects neurons from low-temperature-induced cell death (735). Thus histaminergic trans-

mission during hibernation links energy metabolism, thermogenesis, and behavioral state to higher brain functions according to circadian molecular clock functions and seasonal rhythms (2, 453).

D. Feeding Rhythms and Energy Metabolism

Plenty and remarkably consistent evidence supports a role of brain histamine in food intake and energy metabolism (309, 453, 627). Treatments increasing central histamine such as intracerebroventricular loading with the precursor histidine, or application of H3R antagonists suppress food intake (118, 436, 535, 675) and decrease caloric intake, body weight, and plasma triglycerides in rodents and primates (444). In contrast, application of α -FMH or H1R antagonists increase food intake (186, 535).

The preferential site of histamine-mediated suppression of food intake in the mammalian brain is likely the VMH, a prominent satiety center. Microinfusion of H1R antihistamines into the VMH but not PVN or LH elicits feeding responses and increases both meal size and duration (186, 628). Likewise, electrophoretic application of H1R antihistamines suppresses the firing of glucose-responsive units in the VMH but not LHA or PVN (186). Histamine effects on food intake are linked to a number of other neuroendocrine and peptidergic pathways, including neuropeptide Y, peptide YY, and bombesin (453, 495, 627). Orexigenic actions of orexins/hypocretins (310) and anorexigenic effects of leptin (453, 758) and glucagon-like peptide-1 (GLP-1), which depend on CRH released by PVN neurons (214), are all blunted or absent by pharmacological or genetic loss of H1R function. TRH also suppresses food intake through TRHR2 and H1R (215). Importantly, the PVN and LHA harbor the central command neurons, which also control sympathetic outflow, lipolysis, thermogenesis, and energy expenditure in peripheral tissues (453).

The mesencephalic trigeminal nucleus is another site concerned with food intake (185). Mastication activates histamine neurons (628). Depletion of neuronal histamine from the mesencephalic trigeminal sensory nucleus (Me5) by bilateral injections of α -FMH reduces eating speed and prolongs meal duration but does not affect meal size. Turnover of neuronal histamine in the Me5 is elevated during early phases of feeding followed by histamine surges in the VMH at later stages, the latter being abolished by gastric distension. Mastication-induced activation of histamine neurons in turn suppresses food intake through H1R activation in the PVN and the VMH. Thus histamine is implicated in timing of appetite and feeding behavior likely through interference with components of the circadian molecular clock and food-entrainable oscillators (2, 453). Depletion of neuronal histamine by α -FMH enhances feeding-associated locomotor behavior only in

the phase of the circadian cycle when histamine release is high (145, 627), and H1R-KO mice have disrupted diurnal feeding rhythms before onset of metabolic syndromes and obesity, which can be ameliorated by scheduled feeding (453).

E. Fluid Intake and Balance

Histamine elicits drinking following injection into the cerebral ventricles or into several hypothalamic sites (203, 392). Through H1R, histamine stimulates neurons in the SON that release the antidiuretic hormone AVP (239, 357). The release of AVP causes an antidiuresis (56, 58, 347, 774) and renal sympathetic activation (65). In addition, AVP release is stimulated indirectly via histamine-induced local release of norepinephrine (52). Likewise, electrical stimulation of the TMN in freely behaving rats enhances histamine release in the SON and increases plasma concentration of NE along with eliciting pressor responses and tachycardia, but does not elevate plasma levels of AVP (16). Prolonged (24 or 48 h) dehydration increases synthesis and release of histamine in the hypothalamus (348, 353). Furthermore, blockade of histamine synthesis by α -FMH, activation of presynaptic H3 autoreceptors, or antagonism of postsynaptic H1Rs and H2Rs strongly depress dehydration-induced vasopressin release (348, 353). Dehydration-induced renin release (346, 457) and pressor responses to a peripheral hyperosmotic stimulus appear to be mediated through central histamine activation of sympathetic outflow (14, 15). Brattleboro rats, which lack AVP, have elevated histamine levels in several hypothalamic nuclei but blunted endogenous vasopressin responses, indicating reciprocal interactions between histamine and vasopressin containing neurons (120, 345, 388). Lesions of certain subnuclei (E3 and E4) of the tuberomammillary complex induce strong and persistent polydipsia in rats, independent from food intake (440).

F. Stress

Histamine release is a sensitive indicator of stress (744, 787), and chronic restraint and/or metabolic stress are among the most potent activators of histamine neurons in the TMN (475). Distinct subgroups (E4-E5) of hypothalamic histamine neurons respond to immobility, foot shock, hypoglycemia, and dehydration, suggesting a functional heterogeneity of histaminergic TMN neurons (475). TMN neurons are influenced by a number of neuroendocrine signals (214) and may integrate exteroceptive and interoceptive state cues in the control of stress-induced arousal. Histamine mediates the stress-induced neuroendocrine hormone surges of ACTH, β -endorphin, and AVP from the pituitary (344) and controls stress-related activity of aminergic systems, including seroto-

nin-, norepinephrine-, dopamine-, and acetylcholine-containing neurons (see sect. *viF*). As an integral part of the neural networks generating autonomic patterns (635) histamine neurons interfere with AVP- and CRH-positive sympathetic command neurons (371) in the PVN and LHA (see sect. *viiiD*) (813) to influence sympathoadrenal outflow, cardiovascular functions, and complex stress-related behaviors such as flight-fight or grooming. Histamine injections in the PVN activate the HPA axis through CRH release. Moreover, both histamine and CRH are released from mast cells in the leptomeninges and along brain capillaries during systemic stress emphasizing the intricate interaction between histamine and CRH, and the nervous and immune system (168).

G. Thyroid Axis

Thyroid functions play a role in energy metabolism, thermogenesis, and bone physiology. TRH is synthesized in preoptic, paraventricular, and periventricular neurons, from where it is transported and released into the hypothalamic portal circulation. The majority of the TMN neurons are excited by TRH (673), and hypothalamic neuronal histamine in turn has predominantly inhibitory effects on the hypothalamo-pituitary-thyroid (HPT) axis (356). Histamine decreases TRH release and TSH plasma levels through H2R in both hypothalamic and pituitary targets (477). Cimetidine facilitates cold-induced and TRH-induced TSH responses (501, 771). Systemic L-thyroxine administration, along with rises in T_3 and T_4 levels, increases cortical 5-HT and histamine content, whereas carbimazole treatment lowers histamine, glutamate, and 5-HT levels, suggesting a T_3/T_4 -mediated negative feedback on TRH production by histamine (778). TRH is also a cotransmitter of glutamatergic neurons located in DMH (110) and serotonergic neurons in the raphe implicated in TRH-induced suppression of food intake by histamine (215) and effects on behavioral state (612).

H. Somatotrope Axis

Growth hormone secretion in the pituitary gland is under hypothalamic control of GHRH (facilitation) and GHIH (somatostatin, inhibition), the latter being likely a target for histaminergic interference. Central histamine application suppresses pulsatile GH secretion in rats (513), an effect blocked by anterolateral hypothalamic microdissections eliminating somatostatin but not GHRH innervation (225). The endogenous growth hormone secretagogue receptor ligand ghrelin, a stomach-derived factor implicated in energy homeostasis (738), excites histamine neurons in vitro through inhibition of G protein-coupled inward rectifier K^+ channels (Kir3, GIRK) (39).

Dietary restriction of histidine intake decreases GHRH expression (85).

I. Bone Physiology and Calcium Homeostasis

Histamine controls blood calcium levels through H2R (29, 832), and targeted disruption of HDC leads to an increased bone density in ovariectomized mice by inhibiting osteoclastogenesis and increasing calcitriol synthesis (174). Modulation of somatotrope and brain-bone axis communication by the hypothalamic histamine system may impact bone physiology but also adult stem cell plasticity (700), immunity, and cancer, providing an intriguing link between brain function and tissue homeostasis (79, 730).

J. Reproduction

Histamine effects on brain physiology and function are likely highly gender specific (5). Striking differences in histamine-dependent behaviors and functions in males and females (332, 389) are in line with sex-specific differential properties of histaminergic transmission in decisive brain regions (5, 389). Hypothalamic histamine actions have a well-established role in the neuroendocrine control of GnRH release (356, 389). Central histamine administration activates the hypothalamo-pituitary gonadal axis through excitation of LH-RH releasing neurons in the SON, while having no direct effect on gonadotrope FSH and LH hormone secretion from the anterior pituitary gland (478). In males, these histamine actions are sensitive to H1R and H2R antagonists. In ovariectomized females they are mediated mainly by H1R, whose expression is controlled by estrogens (265, 522). Accordingly, histamine stimulates estrogen-induced but not basal LHRH surges (356, 478). Sex steroids may provide feedback on histamine synthesis and function, although evidence is rather limited in this respect (171). TMN neurons of rats and humans express α -estrogen receptors (171) which may control a positive feed-forward loop from histamine neurons to LHRH neurons in the SON. Clinical observations support this view since LHRH analogs used to treat cancer are potent histamine releasers (405). Castration also increases hypothalamic histamine levels in rats (538).

Histamine is a regulator of immunity and blastocyst implantation during pregnancy, of gonadal development during embryogenesis, of postpartal lactation, and later in adulthood of sex steroid metabolism in many tissues (554). Histamine-deficient HDC-KO mice have elevated testicular and serum androgen levels but reduced testis weight, independent from GnRH expression, and their mating behavior and sexual arousal are strongly impaired (554). Likewise, administration of the H1 antihistamine

astemizole affects testis weight and male reproductive behavior. Histamine may thus play a role in brain masculinization. Lactation implicates prolactin secretion, and histamine promotes short restraint stress-induced prolactin release (356) likely by H2R-dependent inhibition of tuberoinfundibular dopaminergic neurons and/or direct facilitatory effects mediated by α - and β -adrenoreceptors (817). Histamine effects on prolactin release are blocked by H3R agonists. The majority of neurons in the arcuate nucleus (ARC), which receives dense histaminergic innervation, are excited by histamine through H1R (414). The brain histamine system, likely due to its sensitivity to sex steroids and interference with hypothalamo-pituitary gonadal axis functions, plays a role in a variety of sex-specific developmental, reproductive, and behavioral brain functions.

X. HIGHER BRAIN FUNCTIONS

A. Sensory and Motor Systems

In the periphery histamine signals tissue injury and inflammation and is a specific mediator of itch. In the central nervous system it is involved in sensory gating and modulation of pain at subcortical and cortical levels (269, 278) (see sect. XI). Histamine facilitates locomotion depending on sites of injection, dose, and species (533). In the rat, intracerebroventricular injection of histamine induces a transient increase followed by a decrease in locomotor activity. Depletion of brain histamine decreases locomotion. Likewise, chronic loss of H3R function in H3R-KO mice is associated with reduced locomotion (762) and mice lacking histamine (HDC-KO), or the H1R (284) display altered ambulatory activity and reduced exploratory behavior, particularly in a novel environment (556). However, acute pharmacological blockade (likely protean agonism) of central H3R induces modest hyperactivity. Moreover, histamine modulates vestibular functions and postural muscle tone.

B. Mood and Cognition

1. Anxiety and aversion

Pharmacological and genetic studies in rodents indicate that histamine may be a danger response signal promoting anxiety (84). Lesions of the tuberomammillary nucleus reduce anxiety (183), whereas increases in histamine produced by thioperamide are anxiogenic when combined with blockade of H2R by zolantidine (279). The anxiogenic action of thioperamide plus zolantidine is blocked by the H1R antihistamine mepyramine, supporting a convergence on the H1R. L-His-induced avoidance responses are mediated by H1R (375), and infusions of either the H1R antihistamine chlorpheniramine or the

H2R antagonist ranitidine into the nucleus basalis magnocellularis region exert anxiolytic effects (599). Likewise, H1R-KO mice are less anxious than wild-type mice (834), but both H1R-KO and H2R-KO mice show improved amygdala-dependent auditory and hippocampus-dependent contextual fear acquisition (127). The anxiogenic actions of histamine are in keeping with direct excitatory effects in decisive brain targets including midbrain (72), septum, hippocampus, amygdala (301), and cholinergic synapses (60, 559, 619). Local blockade of H3R in the amygdala impairs retention of fear memory, while activation has opposite effects. The protean agonist proxyfan enhances fear memory expression in rats (44), suggesting a low level of constitutive H3R activity. Neither thioperamide nor *R*- α -methylhistamine changes the amount of time spent in the open arms of the elevated plus-maze (567) but inhibits conditioned fear and avoidance responses (60, 559, 619). H3R-KO mice show decreased anxiety to unavoidable threat (614). Chronically decreased histamine levels and reduced histamine release in the amygdala contribute to increased measures of anxiety in ApoE-deficient mice (785). Finally, mice with a global deficiency in HDC behave more anxious than controls (138, 139). Together this suggests a complex role of histamine in anxiety and in reinforcement of anxiety-related behaviors.

2. Pleasure and reward

The effect of brain histamine on primary reward is thought to be mainly inhibitory (716, 801, 857) but is still controversial (70, 71). Consummatory and sexual behaviors are compromised by pharmacological or genetic loss of histamine and histamine-receptor function (138, 139, 453, 554) associated with characteristic neurochemical alterations in dopaminergic and striatal primary reward systems in the brain (192, 801, 857). However, HDC-KO mice (138, 139), similar to rats with TMN lesions (182), also show gender-specific (5) decreased measures of anxiety and improved negatively reinforced learned behaviors. This is in keeping with anxiolytic (834) and memory-enhancing effects of H1R loss of function (127) and the reinforcing and addictive properties of first generation H1 antihistamines (243) (see sect. XI). Thus brain histamine acts in concert with and complementary to both primary reward and punishment systems to influence appetitive and aversive behaviors.

3. Cognition

H1 antihistamines impair cognitive performance in humans, and this action has been largely attributed to sedative effects (723) (see above) resulting from suppression of cholinergic subcortical (334, 335, 828) and cortical activity (60, 603, 828). There is a remarkable specificity of brain histamine in behavioral and cognitive state control. Recordings from TMN neurons in narcoleptic dogs (305)

and healthy mice in vivo (724) (Fig. 21) provide evidence for a dissociation of histamine and hypocretin neuron function in cognitive processing. While the brain histamine system seems to be particularly important for the maintenance of quiet waking and novelty-induced arousal (556, 724), the neighboring hypocretin neurons rather link emotions and motions (680). The control of histaminergic tone through H3R thus emerges as a major drug target for cognitive enhancers (393, 560).

C. Learning and Memory

Histaminergic modulation of learning and memory is evident from lesions and pharmacological interventions in the tuberomammillary (354, 515, 533) and other decisive brain regions (21, 60, 125, 134, 559) and from studies in histamine- and histamine receptor-deficient mice (127, 138, 139, 420). Confusingly, histamine can have both inhibitory and facilitatory effects on learning and memory. Seemingly conflicting evidences may be explained by differences in species and gender (4, 5) but also context- and task-inherent reinforcement contingencies, particularly novelty (139, 556).

Histamine-deficient mice lack the ability to stay awake in a novel environment associated with defects in hippocampal theta rhythm, cortical activation, and episodic object memory (139, 556). Novelty-induced arousal reinforces learned appetitive behaviors, such as conditioned place preference (86, 125, 138, 139, 205), and novelty detection and comparator functions have been attributed to the hippocampus, where histamine exerts powerful effects (80, 81, 234, 659, 662) (see sect. VIII). TM stimulation during learning-related exploratory behavior gates signal flow and increases signal-to-noise ratios in the hippocampus by 1) decreasing EPSPs without affecting pop-spike activity in the dentate gyrus (81, 807), and

2) promoting autoassociative network activity in CA3 (660, 843) and long-term potentiation of excitability and synaptic transmission in the CA1 region (80, 81, 234, 659, 662).

HDC-KO mice show improved negatively reinforced performance in a water-maze (139) and retention of contextual fear memory, along with enhanced hippocampal CA1 LTP before and decreased LTP after training (420). Injection of histamine (icv) immediately after training normalizes conditioned contextual fear responses. Acute histamine infusion into the CA1 region of rats immediately after training, but not later, enhances consolidation of inhibitory avoidance memory through an H2R-dependent mechanism (125). This suggests a narrow time window at which histamine reinforces episodic memory and learned behaviors (139). Thioperamide (an H3R inverse agonist) enhances memory retention when administered after acquisition (539). In the amygdala, H3R activation enhances consolidation of fear memory (92), and H3R antagonists impair fear memory (558) but through protean agonism may also facilitate it (44). Systemic administration of *R*- α -methylhistamine, an H3R agonist, improves spatial memory in rats (618).

Thus brain histamine, associated with heightened states of vigilance, is required to learn the new (86), which (through remembrance of things past) implies discrimination and comparison of what, where, and when in previous and novel contexts (novelty detection) and consolidation of episodic memory (through mechanisms of synaptic plasticity, see sect. VIII).

XI. PATHOLOGY AND PATHOPHYSIOLOGY

No disease entity has so far been linked specifically or selectively to brain histamine dysfunction. Animals with a loss of histamine or histamine receptors (Table 2)

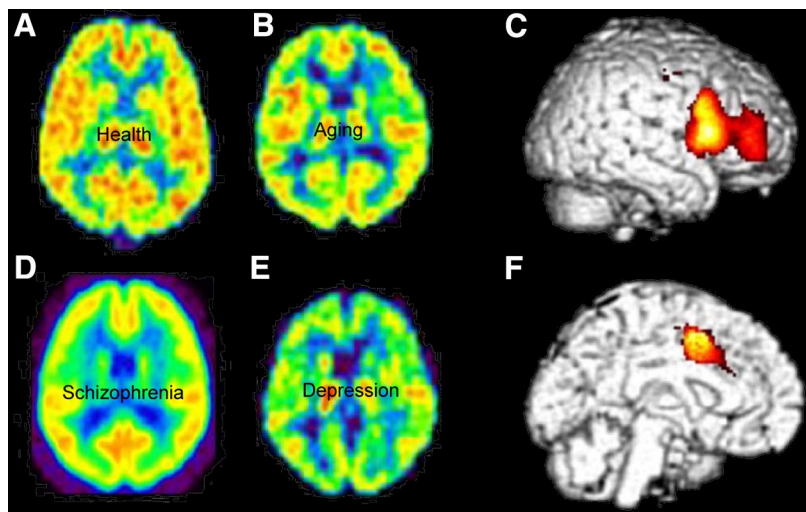


FIG. 21. Prototypic changes of H1R binding in the human brain in health (A and B) and disease (C–F). Note the significant decrease in H1R binding in cortical structures in the aged and diseased brain (B–D). H1R binding in depression was significantly decreased in prefrontal (E) and anterior cingulate cortices (F), correlating with clinical scores of disease severity. [Modified from Yanai and Tashiro (836).]

TABLE 2. *Animal models with a loss of function of histamine-related genes*

Animal Model	Reference Nos.
HDC-KO	528
H1R-KO	284, 835
H2R-KO	360
H1R and H2R double-KO	715
H3R-KO	762
H4R-KO	259

HDC, histamine-deficient animals; KO, knockout mice; H1R–H4R, histamine receptors.

exhibit only subtle abnormalities in basic physiology or behavior. Additional factors must come into play to disclose the role of histaminergic dysfunction in disease. For example, HDC- and histamine receptor-KO mice demonstrate defects in the adaptation of homeostatic and higher brain functions when exposed to various challenges (435, 453, 556). Histamine dysfunction may thus be a precipitating factor for epigenetic disease susceptibility, severity, and progression.

A. Sleep Disorders

Histamine is the major wake-promoting neurotransmitter in the CNS and a key regulator of behavioral state (see above), and thus plays a role in the pathogenesis of sleep disorders. Early descriptions of hypersomnia or insomnia after brain region-specific lesions in the posterior or anterior hypothalamus, respectively, both in animals (510) and humans, such as in von Economo's encephalitis lethargica (794), suggested a central role of the hypothalamus and histamine in sleep control (473). H1R-KO or HDC-KO mice show normal 24-h sleep and wake amounts under undisturbed conditions but a striking inability to stay awake in novel environments, along with slowing of EEG activity, wake fragmentation, and increased REM sleep (272, 556). This phenotype is similar to that of hypocretin-deficient animals, a model of human narcolepsy.

Components of a hypothalamic sleep switch (636, 720), comprising GABAergic inputs from sleep-active VLPO neurons to the histamine neurons in TMN, have been identified as key targets for the sedative effects of general anesthetics (406, 410, 511). Hypnotics selectively targeting VLPO projection sites with specific GABA_A receptor subtypes in histaminergic TMN neurons (667) are warranted for a specific treatment of insomnia, eventually lacking some of the side effects of currently used globally acting benzodiazepines.

Histamine receptors are promising targets for treatment of disorders of behavioral state spanning from hypersomnia (H1R agonists, H3R antagonists) to insomnia

(H1R antagonists, H3R agonists) (47, 473). Most clinically used antihistamines were originally not designed to treat insomnia and have long half-lives and peripheral side effects and are of limited use in sleep medicine (47, 473). Many drugs acting on dopamine and serotonin receptors in the treatment of psychoses are also very effective H1 antihistamines. Hypersomnia is currently treated mainly by drugs enhancing dopaminergic effects such as amphetamines and modafinil, which can also promote wakefulness by activating TMN histamine neurons (642). H3Rs control histaminergic activity and outflow and are thus currently the most promising targets to treat hypersomnia (393). H3R knockouts exhibit excessive muscle activity reminiscent of REM behavior disorder, suggesting a specific contribution of this histamine receptor subtype in the control of REM sleep phenomena and associated disorders, such as narcolepsy (762).

B. Eating Disorders and Metabolic Syndrome

The brain histamine system controls appetite, feeding rhythms, and energy metabolism (see sect. IX) and thus may play a role in eating disorders and metabolic syndromes (309, 453, 627). Compulsive eating in anorexia nervosa, bulimia, or binge-eating syndrome likely relates to histamine effects on brain reward systems and their dysfunction in addiction (see sect. X and below). H3R ligands are clinically tested for application in eating disorders (393, 698).

Histamine- and histamine receptor-deficient animals show hyperphagia and disruption of feeding circadian rhythm and develop obesity, diabetes mellitus, hyperlipidemia, hyperinsulinemia, and disturbance of thermoregulation and cardiovascular functions (187, 311, 453, 739, 848), fundamental marks of metabolic syndromes. Behavioral and metabolic abnormalities produced by depletion of neuronal histamine from the hypothalamus mimic those of obese Zucker rats (628). Grafting the lean Zucker fetal hypothalamus into the obese Zucker pups attenuates those abnormalities. Neuronal histamine regulates food intake, adiposity, and uncoupling protein expression in agouti yellow obese mice (452). Mice with a targeted disruption of the HDC gene show hyperleptinemia, visceral adiposity, decreased glucose tolerance (187), and increased susceptibility to high-fat diet-induced obesity (311). Disturbed H1R-dependent diurnal feeding rhythms and sleep precipitated autonomic dysfunction and late-onset obesity (453, 738), likely implying alterations in humoral arousal and satiety factors (214, 215). The adipocytokine leptin regulates feeding and obesity, partially through brain histamine. Targeted disruption of H1R function attenuates leptin effects on feeding, adiposity, and uncoupling protein expression (454). Hypothalamic H1R and AMPK activation is also responsible for antipsychotic-in-

duced weight gain (453). H3R-KO also display hyperphagia and late-onset obesity associated with hyperinsulinemia and leptinemia (848). H3R antagonists/inverse agonists have thus been developed to counteract body weight gain (393, 848).

Cardiovascular dysfunction and hypertension linked to metabolic syndromes are associated with a wide variety of functional changes in the hypothalamus (137), probably reflecting an integrated compensatory natriuretic response to the kidney's impaired ability to excrete sodium. Several studies in spontaneously hypertensive rats have demonstrated changes in histamine release or turnover (119, 529, 586, 587).

C. Pruritus and Pain

Histamine mediates itch and modulates pain in the periphery and in the CNS. Broad functional overlap but also a striking anatomical and molecular specificity characterizes these distinct sensations (278, 465). In the periphery histamine specifically activates and sensitizes itch-specific nociceptive C fibers (648). Itch and pain appear to employ similar molecular and mechanistic signatures but exhibit largely antagonistic interactions and recruit distinct neural pathways (24). Both histamine and opioids can generate itch, while scratch-induced pain and antidepressants with antihistaminic properties can abolish itch (640).

In contrast to histamine actions on nociceptive fibers, the central histamine system plays a role in antinociception and stress-induced analgesia (95, 269). Antihistaminic properties of antidepressants may in turn contribute to the analgesic effects of these drugs (219, 640). Central sites of itch and pain modulation by histamine include first-order itch-specific lamina I neurons in the dorsal horn of the spinal cord and spinothalamic itch-sensitive pathways (24) up to higher order subcortical and cortical circuitries (149, 481). Histamine applied into the cerebral ventricles or periaqueductal grey is analgesic (208, 442, 752). Analgesic and hyperalgesic effects of central histamine are mediated through H2R and H1R, respectively (442, 443), in keeping with altered pain sensitivity in H1R- and H2R-KO mice (480).

Analgesic or nociceptive effects of many neuropeptides rely on histaminergic transmission. Morphine can increase the release and metabolism of brain histamine when applied systemically or more locally in the periaqueductal grey (48) and slightly depolarizes TMN neurons, whereas the opioid peptide nociceptin causes a hyperpolarization (165), which may contribute to the antagonism of opioid-induced analgesia (131). Histamine release has been shown to be under the control of facilitatory presynaptic μ -opioid receptors (292) and inhibitory κ -opioid receptors (229); the latter are also

gating GABAergic inputs on TMN neurons by orexins/hypocretins (164). Hypocretin-induced antinociception is naloxone insensitive but enhanced in H1R- or H2R-KO mice and under pharmacological blockade of H1R and H2R (480). Reductions in brain histamine levels by administration of α -FMH or H3R agonists promote nociception (442, 443). Increases in brain histamine produced by loading with L-histidine or application of HNMT inhibitors or H3R antagonists have analgesic effects (442, 443). H3R represent a promising target in pain therapy (95).

D. Neuroinflammation

Histamine and histamine receptors cooperate on multiple arms of allergic and autoimmune responses (20, 423, 564). Mice lacking histamine (HDC-KO) have elevated levels of proinflammatory cytokines and develop a more severe experimental allergic encephalomyelitis (EAE), an animal model of multiple sclerosis (MS) (500). HDC in many tissues is downregulated by glucocorticoids, a gold standard in the therapy of inflammatory CNS diseases and known to protect the brain during innate immune responses. A lack of histamine synthesis and downregulation of H1 and H2 receptor mRNA levels by dexamethasone was found in cerebral endothelial cells (329). An antigen-induced release of histamine from mast cells or endocrine cells in sympathetic ganglia can modulate vegetative nervous transmission (810).

The gene locus encoding the H1R is identical to that for *Bordetella pertussis* toxin-sensitization (Bphs), an important autoimmune disease locus, and thus controls both histamine-mediated autoimmune T cell and vascular responses after pertussis toxin sensitization (435). H1R- and H2R-deficient mice have a lower susceptibility to develop EAE (435, 748, 749). H1Rs and H2Rs are reciprocally up- and downregulated on Th1 cells, reactive to myelin proteolipid protein. This challenges pathogenetic concepts of autoimmunity, previously thought to be antipodal to allergy (564). H1R are elevated 4.6-fold in chronic silent cases of MS (423), and H1 antihistamines, approved for treatment of allergy, urticaria, and vestibular dysfunction, may thus also be useful in treating MS (20). EAE is attenuated in mast cell-deficient mice, and increased mast cell-specific proteases are found in both EAE and MS. This suggests a major contribution of mast cells (see sect. III) in inflammatory CNS diseases (142, 751), but recent evidence also highlights the role of the central histamine systems and H3R.

Neuroinflammation is aggravated, and disease severity and progression are enhanced in mice deficient in the H3R (749), which thus not only control brain histaminergic tone but also act as gatekeepers for the immigration of immune cells into the immunoprivileged CNS. Worsening

of inflammatory brain disorders by acute stress (CRH excess) (751) or nutritional-metabolic loads (leptin surges) (500) are in keeping with the sensitivity and function of the brain histamine system in these contexts. Therefore, the brain histamine system and particularly H3R are candidate targets (393) for the development of drugs treating neuroinflammatory and neurodegenerative conditions associated with BBB (151, 749) and/or transmigration of blood cells into the brain (700).

E. Brain Injury and Headache

Histamine plays a role in atherosclerosis, neuroinflammation, plasticity, and degeneration and thus likely contributes to the pathophysiology of brain injury associated with hypoxia (152), ischemia and stroke (256, 428), trauma (427, 484), or neoplasms (391). In all of these conditions, histamine-mediated recruitment of immune cells into damaged tissue and histamine receptor functions have been reported to be altered (256, 428). H1R and H2R on endothelial cells directly participate in acute hyperemic response to physiological and pathological stimuli that require BBB opening (117, 126, 226, 714, 749) yet without affecting cerebrovascular protein permeability (450). Glucocorticoids, such as dexamethasone used to treat brain edema, downregulate vascular H1R and H2R (329). Cimetidine, an H2R antagonist, exhibits unexpected properties as an antitumor agent with potential for the treatment of glioblastoma (391) likely by antagonizing growth-promoting and immunomodulatory histamine effects.

Moreover, histamine interferes with neurovascular and BBB functions (151, 308, 749) implicated in aseptic neurogenic inflammations underlying vascular headaches. Histamine acts on both peripheral and central (154, 276, 282) components of the trigeminovascular system, which includes trigeminal nuclei, ganglia (737) and nerve terminals, blood vessel (12) endothelial, and mast cells (396, 750). Histamine released from vascular endothelia promotes NO and PGE₂ synthesis (12) and released from mast cells activates and sensitizes a subset of mechanoin-sensitive nociceptive afferents in the meninges (654, 750), along with blood vessel dilatation (153, 384). Intravenous injection of histamine is a trigger of cluster headache (516), migraine (385), and neuralgias (458). Cluster headache is also called "histaminic cephalalgia" (Horton's headache) (169) and is associated with a hypothalamic dysfunction, disturbed biological rhythms, and sleep (489, 788). It can be precipitated by NO and alcohol, both of which have been implicated with histaminergic functions. However, antihistamines do not seem to be an effective treatment of acute primary headaches. In contrast, triptans (5-HT_{1B/D} agonists) provide a specific pharmacological treatment of migraine and other vascular head-

aches (397). Histamine may thus interfere with primary headaches indirectly, through actions on serotonergic transmission or other migraine susceptibility gene products (314). The view that migraine is a failure of normal sensory processing (209) is compatible with the role of the central histamine system in sensory gating, itch, and antinociception (270, 480). Clinical studies evaluating H3R agonists in neurogenic edema and migraine prophylaxis are under way (393, 476).

F. Encephalopathy

Histamine likely plays a pathophysiological role in many encephalopathies, particularly those due to metabolic failure. Histamine levels in the brain are determined by the availability of histidine (see sect. iv), which increases severalfold in patients with liver cirrhosis and in animal models of that disease with a portacaval shunt (179). This results in highly (up to 13-fold) elevated brain histamine levels, especially in the hypothalamus, along with modest changes in tele-methylhistamine and histamine-*N*-methyltransferase activity (179, 180). Altered histaminergic receptor physiology (H1R upregulation) is responsible for characteristic changes in circadian rhythms and sleep EEG (430, 431), early signs of hepatic encephalopathy. H1R antihistamines have thus been proposed for prevention and treatment of circadian rhythm and sleep abnormalities caused by histaminergic hyperactivity (430) that may contribute to disordered thalamocortical processing and clinical symptoms of human hepatic encephalopathy. Likewise, portacaval shunted rats exhibit behavioral abnormalities prototypic for hepatic encephalopathy along with a striking impairment in H3R-mediated corticostriatal synaptic long-term depression (674).

The release of histamine from nerve terminals and histamine together with other vasoactive substances from granulocytes may be responsible for thiamine deficiency-induced vascular breakdown and perivascular edema within the thalamus of rats (383). This suggests a significant and regionally selective role of histamine in the development of thalamic lesions in Wernicke's encephalopathy, which is associated with shrinkage of hypothalamic mamillary bodies in humans. Mamillary abnormalities have also been observed in schizophrenia (74), and thiamine deficiency promotes muricidal behavior in rats, an animal model of depression (533) (see below). Thus brain histamine likely plays a role in the pathophysiology of many brain disorders.

G. Movement Disorders

Histamine levels in the brains of Parkinson patients are selectively increased in the putamen, substantia nigra, and external globus pallidus (613). Tele-methylhistamine

levels are unchanged in the substantia nigra (613), suggesting limited histamine transport capacity. The TMN neuron morphology (504) and HDC activity (195) appear normal in patients suffering from Parkinson's disease, but morphology and density of histaminergic fibers in the substantia nigra suggests sprouting of histamine-containing terminal fibers around the degenerating nigral neurons (28). In the human basal ganglia, H3R expression is normally strong in the putamen, moderate in the globus pallidus, and low in the substantia nigra (27). H3R binding is abnormally high in the Parkinsonian substantia nigra (26), and the same phenomenon is seen in rats after depletion of nigrostriatal dopamine stores using 6-OHDA (624). H3R activation impacts GABA and serotonergic outflow in the indirect and direct basal ganglia pathways (198, 364, 753, 855), and the signal transduction of H3Rs suggests that they are promising drug targets for the therapy of basal ganglia disorders and neurodegenerative diseases (62, 785). In Huntington's but not Parkinson's disease, there is a specific loss of H2R particularly in the putamen and globus pallidus in keeping with animal data on neurotoxin-lesioned striatal neurons (212, 449).

H. Mood Disorders

1. Schizophrenia

Basic science and clinical studies suggest a role of brain histamine in schizophrenia. Schizophrenics, especially those with predominantly negative symptoms, have elevated levels of *N*-tele-methylhistamine, the major histamine metabolite in the cerebrospinal fluid (593, 594) in line with enhanced histamine turnover in most genetic, pharmacological, and lesion-based animal models of schizophrenia (78, 128, 133, 170, 181). H1R binding sites are decreased in the frontal and cingulate cortex in post mortem brain samples (503) or PET studies (294, 836) (Fig. 21), along with abnormalities in hypothalamic paraventricular and mamillary body morphology (211). Together this implies increased histamine release and turnover in schizophrenia. Famotidine, an H2R antagonist, reduced negative symptoms in schizophrenics (321, 447), irrespective of drug interactions with antipsychotic medication (597). However, none of the polymorphisms in H2R (288, 446, 536) or HNMT (833) has been consistently linked to psychotic symptoms in schizophrenia.

All antipsychotics act on dopamine D2R, supporting the proposition of dopaminergic supersensitivity as a major factor in disease susceptibility and pathogenesis (656) and of novel pharmaceutical targets interfering with both brain dopamine and histamine systems (365, 671). Moreover, *N*-methyl-D-aspartate receptor antagonists enhance histamine neuron activity in rodent brain (170), suggesting that brain histamine contributes to glutamatergic dysfunction in schizophrenia. Thioperamide has antipsychotic-like

properties in mice (13). Ciproxifan, a histamine H3R antagonist/inverse agonist, potentiates neurochemical and behavioral effects of haloperidol in the rat (575) and modulates the effects of methamphetamine on neuropeptide mRNA expression in the rat striatum (574). Sedative antipsychotics bind to H1R, while atypical antipsychotics have H3R antagonistic properties increasing histamine outflow and turnover (167, 393, 615). Activation of hypothalamic H1R and AMPK pathways are responsible for weight gain induced by atypical neuroleptics (260, 336, 370).

2. Depression

Pharmacological or genetic loss of histamine or histamine receptor function in animals produces phenotypes that model human depression (127, 289, 508, 692). Histamine neurons in the TMN are sensitive to many, if not all, neuroendocrine signals implicated with depression, including biogenic amines, peptides, and steroid hormones, as well as antidepressant medication (see sect. VII). Histamine neurons are strongly excited through 5-HT_{2C}, a serotonin receptor that undergoes posttranscriptional editing (665) that correlates with suicide (647). Noradrenergic α 2-receptors increase GABAergic inhibition of TMN neurons (512, 707), and interactions with peptidergic influences, e.g., hypocretins (163, 164), CRH, and steroid hormones, may be implicated in neuroendocrine and coping abnormalities in depression.

PET studies using [¹¹C]doxepin, an antidepressant with high affinity to H1R, revealed reduced H1R binding in frontal and prefrontal cortices, and the cingulate gyrus correlating with the severity of clinical depression (325, 836) (Fig. 21). Anomalies in histamine metabolism (methylation) may account for endogenous depression in humans (190), and the association of depression and atopy (757) is in line with convergent roles of histamine in immune and stress responses (704, 751).

Many antidepressants have H1R and H2R antihistaminic properties (219, 602, 611), which likely do not account for their therapeutic efficacy but a number of serious adverse effects, including sedation, weight gain, and cardiovascular dysfunctions. Dose-dependent H1 antihistaminic properties of antidepressants may be useful to treat insomnia (685) and endogenous histamine, and H1R agonists have antidepressant-like properties (381). Some of the first-generation antihistamines act as serotonin reuptake inhibitors in animals and humans (326). Some H3R antagonists share this action (46, 567). Notably, all currently available antidepressant pharmacological interventions have a rather slow onset (2–3 wk). In contrast, sleep deprivation exerts well-known rapid but transient antidepressive effects that may rely on a histaminergic mechanism in arousal control (793). Modulation of histaminer-

gic transmission may thus prove to be useful in the treatment of depression and related mood disorders.

I. Dementia

In Alzheimer's disease, several subcortical ascending projections, including the histaminergic neurons, display degeneration and tangle formation (718). In the hypothalamus, neurofibrillary tangles occur exclusively in the tuberomammillary nucleus accompanied by reduced numbers of large neurons (9, 11, 505). Histamine and metabolite levels in the spinal fluid increase with increasing age (595), in contrast to other amines. A decline in histamine levels and/or HDC activity has been seen in Alzheimer's disease (287, 549) and Down's syndrome (337, 649, 658). Functional imaging studies (Fig. 21) show decreased brain H1R occupancy in Alzheimer's disease compared with age-matched healthy controls (836), in keeping with cognitive impairments induced by the H1R antihistamine chlorpheniramine (530). Long-term treatment with H2R antagonists did not reveal consistent protection in Alzheimer's disease (850).

J. Epilepsy

The brain histamine system protects against convulsions in a number of animal epilepsy models (106, 107, 847). Treatments that elevate brain histamine levels ameliorate a form of hereditary temporal lobe epilepsy that can be elicited by weekly vestibular stimulation, while intraperitoneal injection of the H1 antihistamine diphenhydramine aggravates seizures (846). Likewise, lesion of the tuberomammillary nucleus E2 region attenuates postictal seizure protection (303), while blockade of H1R promotes convulsions in a number of animal models (106, 107, 184, 319, 800, 846) and humans (277, 303, 684, 697, 795). Proconvulsant effects of H1R antihistamines have been observed particularly in children (684, 697), and seizures may also be promoted by treatment with H2R antagonists (famotidine) (795). Blockade of H3R, which facilitates histamine release, is anticonvulsant (374, 846). The antiepileptic network effects of histaminergic transmission probably rely on H1R-mediated excitation of interneurons and inhibition of hippocampal principal neurons that outbalance excitatory histamine effects on cortical excitability, potentiation of NMDA receptors, and the H2R-mediated potentiation of excitability. Moreover, H1R activation, in line with their antiepileptic properties, is neuroprotective in vitro (129, 302, 374, 418) and restrains excitotoxic glutamatergic actions (129, 140, 659, 844). On the other hand, histamine can clearly promote excitotoxicity through its excitation potentiating actions, especially on the NMDA receptor (641, 687, 844). The spatiotemporal pattern of histamine receptor activation may deter-

mine cell fate by activation of neuroprotective or neurodegenerative signal transduction pathways (62, 336, 659).

K. Vestibular Disorders

Antihistamines are effective treatments of motion sickness and emesis (684, 728, 729), likely by blocking histaminergic signals from vestibular nuclei to the vomiting center in the medulla (57, 727). Consistent with the role of the brain histamine system in autonomic responses, vestibular nucleus-induced hypothalamic neuronal activity in the guinea pig is modulated by H1R and H2R antihistamines (283). Moreover, histamine plays a role in the central plasticity encompassing vestibular compensation (429, 526, 542, 756). This includes long-term changes in expression of HDC in the TMN and H3R binding in vestibular nuclei. Betahistidine is a partial agonist at H1R and antagonist at H3R (338, 829), upregulating histamine turnover and release (755). It inhibits histaminergic excitation of medial vestibular neurons (802) and is thus frequently prescribed for treatment of motion sickness and vertigo.

L. Addiction and Compulsion

Addiction and compulsion likely rely on the usurpation of biological mechanisms controlling learning and memory and their reinforcement through pleasure and aversion. Histaminergic modulation of either function (see sects. ix and x) may also precipitate drug dependence, addiction, and compulsion.

Histamine-dependent modulation of pain and memory functions by novelty-induced arousal may be particularly relevant for the vicious cycle of relapse and withdrawal, which includes hyperarousal, pain, and psychosis (delirium). Many of the drugs interfering with behavioral and metabolic state (benzodiazepines, alcohol, morphine, cannabinoids, cocaine) are addictive and interfere with TMN histamine neuron activity (509) (see sect. vi). Detailed mechanisms of how the brain histamine system is implicated in addiction and compulsion are poorly understood but likely rely on histamine effects in decisive brain targets (hypothalamic hypocretin and CRH neurons, VTA, accumbens, hippocampus) (see sect. viii). H3R cooperate with dopamine D2 receptors in the regulation of striatal gene expression (573). Related interactions of histamine with dopamine, other amines, GABA, and glutamate (659, 662) may be relevant for both learning and memory, as well as addiction and compulsion.

Rats selected for ethanol preference display highly elevated brain histamine levels and turnover, increased density of histamine-immunoreactive nerve fibers, lower H1R expression, and lower H1R and H3R binding in some brain areas (416). Thioperamide and clobenpropit reduce

and *R*- α -methylhistamine increases ethanol intake in these rats, suggesting that H3R regulate operant responding to ethanol. H3R antagonist-induced dopamine release was not further increased by ethanol. In contrast, rats bred selectively for sensitivity to ethanol-induced motor impairment display significantly lower brain histamine levels than the ethanol-tolerant rat line and show higher receptor expression and G protein signaling of H1R and H3R (417). Lowering the brain histamine levels significantly increases ethanol sensitivity of tolerant rats. In keeping with these data, a HMNT polymorphism has been linked to alcoholism in humans (609).

XII. CONCLUSION AND OUTLOOK

Histamine, the product of histidine decarboxylation, is an evolutionary conserved signaling molecule. It acts as a powerful stimulant of gastric acid secretion, immune modulation, bronchoconstriction, vasodilation, and neurotransmission. The hypothalamic histamine neurons are deeply involved in basic brain and body functions linking behavioral state and biological rhythms with vegetative and endocrine control of body weight and temperature. Acting at the gate for consciousness, they keep the CNS ready to react and the organism alert. Histamine binds to and acts through four identified histamine receptors and a polyamine binding site on glutamatergic NMDA receptors. Through H1R and H2R, it mediates excitation and (long-term) potentiation of excitation, while the H3R autoreceptors provide feedback control of histamine synthesis, release, and electrical activity. As heteroreceptors they also control exocytosis of most other transmitter systems, making them a prime target for pharmaceutical research and development. Among histamine's role in many homeostatic and higher integrative brain functions, novelty-induced attention and arousal are of major importance for adaptation to changing environments by comparing news with the remembrance of things past. This is decisive for brain development, physiology and pathophysiology, danger recognition, and survival.

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With this review, we honor Jack Peter Green, who died in New York on February 10, 2007. He was the unwearied advocate for the histaminergic system in the brain during the times of neglect.

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