HISTAMINE

Chemically histamine is a biogenic amine. Its role in local immune responses as well as in the regulating physiological functions has been known since long. Its role as a neurotransmitter was identified in 1970's. It triggers the inflammatory response. As part of an immune response system, it is produced by basophils and by mast cells found in nearby connective tissues. It increases the permeability of the capillaries to white blood cells and other proteins, in order to allow them to engage foreign invaders in the infected tissues. It is found in virtually all animals. Histamine is best known as a mediator of allergic reactions, but it is now recognized to participate in numerous other normal and pathologic processes. The sensitivity and response of a particular cell to histamine depends upon which type of histamine receptor is present on that cell. Many of the signs of allergic reaction result from the ability of histamine to affect blood vessels, inducing increased blood flow, vasodilatation and increased vascular permeability

Histamine is synthesized in all tissues, but is particularly abundant in skin, lungs and gastrointestinal tract. Mast cells, which are present in many tissues, are a prominent source of histamine, but histamine is also secreted by a number of other immune cells. Mast cells have surface receptors that bind immunoglobulin E, and when antigen cross links IgE on the mast cell surface, they respond by secreting histamine, along with a variety of other bioactive mediators. (Fig 10.1).

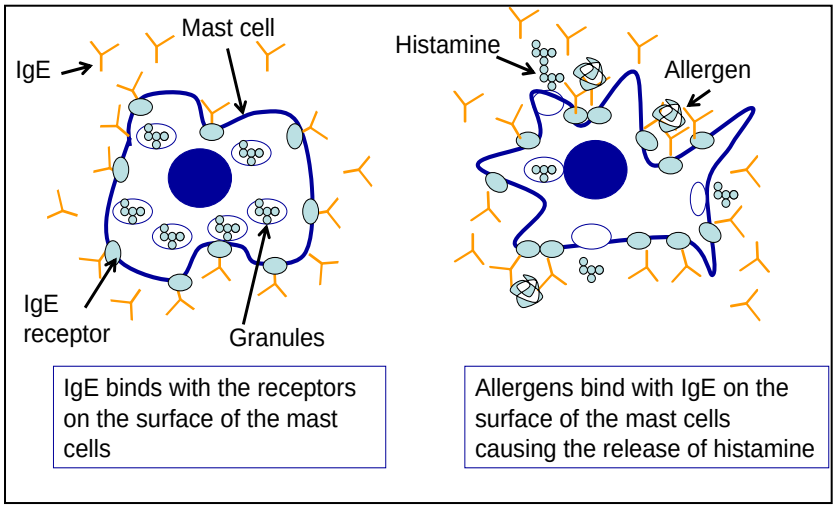

FIG 10.1

LOCALIZATION AND RELEASE OF HISTAMINE: IGE LOCALIZED ON THE SURFACE OF THE MAST CELLS BINDS TO ALLERGENS RESULTING IN THE RELEASE OF HISTAMINE.

PHYSIOLOGIC AND ALLERGIC EFFECTS OF HISTAMINE

An example of systemic effects of histamine is histamine poisoning. This effect is seen following consumption of fish, commonly tuna that have spoiled and within which bacteria have generated abundant quantities of histamine from histidine in muscle protein. Consumption of such spoiled fish results in the rapid development of a variety of clinical signs, including headache, sweating, diarrhea, a flushed face, and vomiting, all resulting from systemic exposure to histamine.

Histamine plays a pivotal role in many types of allergic and inflammatory processes. The source of histamine in such cases is tissue mast cells. The magnitude of such problems depends on the route of exposure (local or systemic), sites of exposure (inhaled or cutaneous), the dose of allergen, and the degree of previous sensitization to the allergen.

In addition to allergic reactions, histamine has significant effects on many aspects of immune system. Among other things, histamine influences immune cell maturation and activation, secretion of several cytokines, and chemotactic responses of cells.

Hydrochloric acid is secreted in abundance by parietal cells embedded in the epithelium of the stomach. One of the principle stimuli for secretion of acid by parietal cells is histamine, secreted from neighboring enterochromaffin cells. The histamine receptor on parietal cells is the H_2 type, and blocking the binding of histamine to this receptor is a widely used method for suppressing gastric acid secretion. Smooth muscles, around bronchi in the lungs and within the intestinal tract respond to histamine stimulation by contraction.

EFFECTS OF HISTAMINE IN THE NERVOUS SYSTEM

Histamine have had a great, although indirect, historical importance in the development of neuropsychopharmacology. Histamine acts as a neurotransmitter within the central nervous system. The (histaminergic) neurons are localized in some regions of the brain, but those neurons

send axons widely throughout the brain. Histamine appears to modulate a number of important processes in the brain, including wakefulness, cognitive ability and food consumption.

Indeed, the discovery of both the neuroleptic and tricyclic antidepressant drugs in the 1950s was derived from the clinical study of behavioral actions of "antihistamines", a class of anti allergic drugs now designated as H1-receptor antagonists.

SYNTHESIS, STORAGE, RELEASE AND DEGRADATION OF HISTAMINE IN THE BRAIN

Histamine is a small molecule derived from the decarboxylation of the amino acid histidine. The decarboxylation of the amino acid histidine is catalyzed by the enzyme L-histidine decarboxylase (Fig 10.2). Once formed, histamine is stored in the synaptic vesicles. Histamine released into the synapses is broken down by histamine-N-methyltransferase.

As we have seen in previous chapters that the synthesis of neurotransmitters is regulated by multiple factors including the availability of precursor and the activity of rate limiting synthesizing enzyme. In case of histamine, the availability of precursor is one of the mechanism by which synthesis of histamine is regulated. Thus administration of histamine has been shown to increase the levels of histamine in the brain. Depolarizing stimuli likewise stimulate the synthesis of histamine in the brain. The neurotransmitter is released in the synaptic cleft by mechanism dependent on the entry of Ca^{+2} ions.

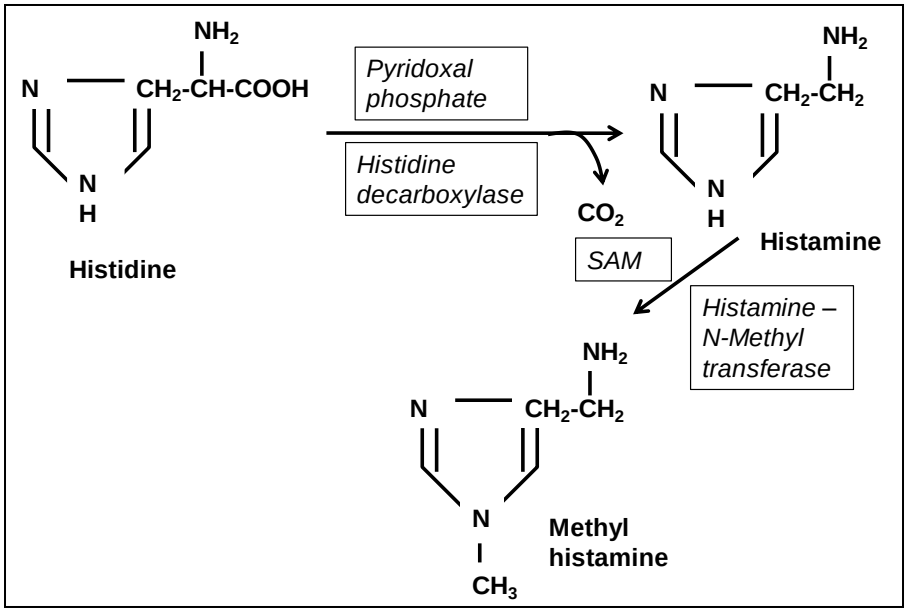

FIG 10.2

SYNTHESIS AND INACTIVATION OF HISTAMINE: HISTAMINE IS SYNTHESIZED FROM THE AMINO ACID HISTIDINE BY THE ENZYME HISTIDINE DECARBOXYLASE; THE IMMEDIATE CATABOLIC PRODUCE IS METHYL HISTAMINE

HISTAMINE RECEPTORS AND RECEPTOR ANTAGONISTS

Four histamine receptors have been identified, all of which are G protein-coupled receptors. These different receptors are expressed on different cell types and work through different intracellular signaling mechanisms, which explain, at least at a simple level, the diverse effects of histamine in different cells and tissues.

The first histamine antagonists - antihistamines - competitively blocked the binding of histamine to H_1 receptors, and have been used for many years in "cold pills" and sleeping aids. Examples of H_1 receptor antagonists include diphenhydramine (Benadryl) and loratadine (Claritin). Interestingly, discovery of new histamine receptors largely followed the findings that the H_1 antagonists did not block all actions of histamine. For example, H_1 receptor antagonists do not effect secretion of gastric acid because that response is due to binding of histamine to H_2 type receptors. Receptor antagonists for H_3 and H_4 receptors are being investigated because of their

potential benefit for function of brain and immune system. A brief summary of all these receptor types is given in table 10.1.

Table 10.1

HISTAMINE RECEPTOR TYPES AND THEIR FUNCTIONS

Receptor Type	Major Tissue Locations	Major Biologic Effects
H_1	smooth muscle, endothelial cells and CNS	Acute allergic responses such as vasodilation, broncho constriction, also involved in allergic rhinitis symptoms, motion sickness; sleep regulation.
H_2	gastric parietal cells	secretion of gastric acid
H_3	central nervous system	modulating neurotransmitter (histamine, noradrenaline and acetylcholine release
H_4	Mast cells, eosinophils, T cells, dendrites	regulating immune responses

MODULATION OF HISTAMINE SYNTHESIS AND RELEASE

The autoreceptors-regulated modulation of histamine synthesis in, and release from, brain neurons is now well documented. It was initially demonstrated in brain slices or synaptosomes after labeling the endogenous histamine pool using the 3H-precursor. Exogenous histamine decreases the depolarization-induced formation and release of [3H] histamine. Analysis of these responses led to the pharmacological definition of H3 receptors. Autoregulation was found in various brain regions known to contain histamine nerve endings, which suggested that all terminals were endowed with H3 autoreceptors. Regulation of histamine synthesis has been also observed in the posterior hypothalamus. Tuberomammillary neurons themselves are sensitive to histamine and to an H3-receptor agonist which inhibits their firing by means of hyperpolarization accompanied by an increased input resistance. This may indicate the existence of autoreceptors at the level of histaminergic perikarya or dendrites.

Galanin, a putative co-transmitter of a subpopulation of histaminergic neurons, regulates histamine release only in regions known to contain efferent of this subpopulation; that is, in hypothalamus and hippocampus but not in cerebral cortex or striatum. In brain slices, galanin also hyperpolarizes and decreases the firing rate of tuberomammillary neurons. It is not known, however, whether these galanin "autoreceptors" modulate galanin release from histaminergic nerve terminals. Other putative co-transmitters of histaminergic neurons failed to affect [3H] histamine release from slices of rat cerebral cortex.

[3H] Histamine synthesis and release are inhibited in various brain regions by stimulation of not only autoreceptors but also α2-adrenergic receptors, M1-muscarinic receptors and κ-opioid receptors. Muscarinic receptors also inhibit endogenous histamine release in the hypothalamus. Since these types of regulation are also observed with synaptosomes, all of these receptors presumably represent true presynaptic heteroreceptors. In contrast, histamine release is enhanced by the stimulation of nicotinic receptors in rat hypothalamus and by μ-opioid receptors in mouse cerebral cortex.

Some molecular mechanisms regulating neuronal histamine dynamics remain unclear. No histamine transporter could be found, and a direct feedback inhibition of histidine decarboxylase by histamine has been excluded.

CHANGES IN HISTAMINERGIC NEURON ACTIVITY

Both neurochemical and electrophysiological studies indicate that the activity of histaminergic neurons is high during arousal. In rat hypothalamus, histamine levels were low, whereas synthesis was high during the dark period, suggesting that neuronal activity was enhanced during the active phase. Histamine release from the anterior hypothalamus of freely moving rats, evaluated by *in vivo* microdialysis, gradually increased in the second half of the light period and was maintained at a maximal level during the active phase. Such state-related changes were also found in single-unit extracellular recordings performed in the ventro-lateral posterior hypothalamus of freely moving cats. Neurons with properties consistent with those of histaminergic neurons exhibited a circadian rhythm in their firing rate, falling silent during deep slow-wave or paradoxical sleep. Tuberomammillary histaminergic neuron activity could be inhibited by a GABA ergic pathway, originating in the ventro-lateral preoptic area that was activated during sleep.

A feeding-induced increase in the activity of histaminergic neurons has also been shown by microdialysis performed in the hypothalamus of conscious rats. Changes in the metabolism and release of histamine observed *in vivo* after occlusion of the middle cerebral artery in rats suggest that the histaminergic activity is also enhanced by cerebral ischemia.

Inhibition mediated by H3-autoreceptors constitutes a major regulatory mechanism for histaminergic neuron activity under physiological conditions. H1 and H2 receptors are apparently not involved. Administration of selective H3 receptor agonists reduces histamine turnover and release, as shown by microdialysis. In contrast, H3-receptor antagonists enhanced histamine turnover and release *in vivo* and histidine decarboxylase activity in various strains of mice, suggesting that these autoreceptors were under tonic stimulation by endogenous histamine.

Agents inhibiting histamine release *in vitro*, via stimulation of presynaptic α2-adrenergic or muscarinic heteroreceptors, reduce histamine release and turnover *in vivo*. However, systemic administration of antagonists of these receptors does not generally enhance histamine turnover, suggesting that heteroreceptors are not tonically activated under basal conditions.

Activation of central nicotinic, and 5-HT1A serotonergic receptors inhibited histamine turnover and activation of D2 dopaminergic receptors enhanced histamine release in vivo, but the presynaptic location of these receptors remains to be demonstrated. Histamine turnover in the brain was also rapidly reduced after administration of various sedative drugs such as ethanol, barbiturates and benzodiazepines. The effect of the latter compounds may result from their interaction *in vivo* with GABA receptors present on nerve endings of a subpopulation of histaminergic neurons containing GABA.

In contrast, stimulation of μ–opioid and NMDA receptors enhanced histamine release and turnover in brain. Morphine increased histamine release in the periaqueductal gray. The reported effects of reserpine on brain histamine turnover are inconsistent: both enhancement and inhibition have been reported.

EFFECTS ON NASAL MUCOSA

Increased vascular permeability causes fluid to escape from capillaries into the tissues, which leads to the classic symptoms of an allergic reaction – a runny nose and watery eyes. Allergens can bind to IgE-loaded mast cells in the nasal mucosa, which leads to three clinical

responses: sneezing results from histamine-associated sensory neural stimulation; hyper secretion from glandular tissue occurs; nasal mucosal congestion results due to vascular engorgement associated with vasodilation and increased capillary permeability.

AROUSAL, ATTENTION AND LEARNING

A large body of experimental evidence has accumulated to indicate that histaminergic neurons play a critical role in cortical activation and arousal mechanisms.

The cell bodies of neurons which release histamine are found in the posterior hypothalamus, in various tuberomammillary nuclei. From here, these histaminergic neurons project throughout the brain, to the cortex through the medial forebrain bundle. Histaminergic action is known to modulate sleep. Classically, antihistamines (H_1 histamine receptor antagonists) produce sleep. Likewise, destruction of histamine releasing neurons, or inhibition of histamine synthesis leads to an inability to maintain vigilance. Finally, H_3 receptor antagonists increase wakefulness.

It has been shown that histaminergic fire rapidly during waking, fire more slowly during periods of relaxation/tiredness and completely stop firing during REM and non-REM sleep. The cell firing starts again just before an animal shows signs of waking.

Intra-cerebral injection of histamine in the cat ventro-lateral hypothalamus, where the density of histaminergic axons is high, increased wakefulness via stimulation of postsynaptic H1 receptors. Endogenous histamine presumably plays a similar role, since inhibition of its synthesis by an L-histidine decarboxylase inhibitor, inhibition of its release by an H3-receptor agonist, or inhibition of its action by an H1-receptor antagonist all increase deep, slow-wave sleep and decrease wakefulness in several animal species. Conversely, inhibitors of histamine methylation or H3-receptor antagonists, which facilitate histamine release, both increased arousal. The role of histaminergic neurons in arousal was also shown by the decreased wakefulness following lesions of the posterior hypothalamus, particularly those lesions aimed at destruction of the tuberomammillary nucleus.

The "arousing effect" of histamine may well be mediated by the cellular actions of H1 and H2 receptors. Accordingly, in humans, many H1 receptor antagonists induce drowsiness, impair performances requiring attention and increase the tendency to sleep—effects which are

stereo selective. As a consequence, these compounds are common ingredients in over-the-counter sleeping pills. New "antihistamines", that do not block cerebral H1 receptors, are devoid of sedative properties. A rather large number of antidepressant (e.g., mianserin or doxepin) and antipsychotic agents (e.g., clozapine) display high H1-receptor antagonist potency, a property that presumably accounts for their sedative side effects. In mutant mice lacking H1 receptors, complex behavioral changes were observed; the expected impairment of locomotor activity in the dark period was accompanied by increased locomotion in the light period.

CONTROL OF APPETITE

Weight gain is often experienced by patients receiving H1 antihistamines or tricyclic antidepressants that have potent H1-receptor antagonist properties. This may reflect an inhibition of feeding exerted by histamine neurons that project to the ventromedial and paraventricular hypothalamic nuclei, as shown by the effects of histamine synthesis inhibitors or H3-receptor ligands. In addition, the extracellular concentration of the amine in rat hypothalamus increases during feeding.

POTENTIAL ROLE IN NEUROPSYCHIATRIC ILLNESSES

Among the various approaches that tend to establish the implication of other aminergic neuronal systems in neuropsychiatric diseases, so far only a few have been applied to histamine. However, elevated levels of methyl histamine in cerebrospinal fluid suggest increased central histaminergic activity in patients with chronic schizophrenia.

Post mortem studies of basal ganglia from patients with Parkinson's disease or in a rodent model of this disease showed no change in the activity of the histamine-synthesizing enzyme.

Patients with Alzheimer's disease show numerous neurofibrillary tangles and typical senile plaques in the tuberomammillary area. It is not clear, however, whether the number of histamine-immunoreactive neurons is decreased. Because conflicting data have been reported concerning histamine levels in such patients, a role of histamine in the etiology of Alzheimer's disease remains doubtful. In addition, it may be significant that 9-amino-1,2,3,4-tetrahydroacridine (THA), an anti cholinesterase that was found to be useful in Alzheimer's disease, is also a rather potent inhibitor of histamine methylation. In addition, an H_3-receptor antagonist improved learning deficits in mice.

The effects of antipsychotics at dopamine receptors strongly suggested the role of dopamine in schizophrenia. In contrast, the interactions of psychotropic drugs with histamine receptors are of limited help for deducing the role of histaminergic neurons in psychiatric illnesses. Over a decade ago it was proposed that the cerebral H_2 receptor are an important target for most tricyclic and other antidepressant drugs that interact with relatively high affinity with the receptor coupled to the cyclase. A number of side effects (e.g., sedation or weight gain) of several antidepressant drugs, as well as some neuroleptics, are attributable to the blockade of cerebral H_1 receptors. The affinity of the atypical antipsychotic drug clozapine at the H_3 receptor is in the same range as at D2/D3 dopamine receptors, but the therapeutic implications of this observation—if any—is unclear.

Unfortunately, the effects of drugs able to stimulate the three cerebral histamine receptor subtypes or to block H_2 or H_3 receptors in neuropsychiatric diseases are not known. Therefore, these receptors remain important potential targets for novel classes of psychotropic agents.

Nonsteroidal anti-inflammatory drugs (NSAIDs) produce their therapeutic activities through inhibition of cyclooxygenase (COX), the enzyme that makes prostaglandins (PGs). They share, to a greater or lesser degree, the same side effects, including gastric and renal toxicity. Recent research has shown that there are at least two COX isoenzymes. COX-1 is constitutive and makes PGs that protect the stomach and kidney from damage. COX-2 is induced by inflammatory stimuli, such as cytokines, and produces PGs that contribute to the pain and swelling of inflammation. Thus, selective COX-2 inhibitors should be anti-inflammatory without side effects on the kidney and stomach. Of course, selective COX-2 inhibitors may have other side effects and perhaps other therapeutic potential. For instance, COX-2 (and not COX-1) is thought to be involved in ovulation and in labor. In addition, the well-known protective action of aspirin on colon cancer may be through an action on COX-2, which is expressed in this disease. Moreover, NSAIDs delay the progress of Alzheimer's disease. Thus, selective COX-2 inhibitors may demonstrate new important therapeutic benefits as anticancer agents, as well as in preventing premature labor and perhaps even retarding the progression of Alzheimer's disease.