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Histamine and Histamine Antagonists

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DRUG LIST

GENERIC NAME	PAGE	GENERIC NAME	PAGE
Brompheniramine	454	Diphenhydramine	454
Carbinoxamine	454	Famotidine	455
Cetirizine	453	Fexofenadine	453
Chlorpheniramine	454	Hydroxyzine	454
Cimetidine	455	Loratadine	453
Clemastine	454	Meclizine	455
Cromolyn sodium	455	Nedocromil	455
Cyclizine	455	Promethazine	455
Cyproheptadine	454	Pyrilamine	455
Desloratadine	453	Ranitidine	455
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HISTAMINE

Sinus problems, hay fever, bronchial asthma, hives, eczema, contact dermatitis, food allergies, and reactions to drugs are all allergic reactions associated with the release of histamine and other autocoids, such as serotonin, leukotrienes, and prostaglandins. Histamine release is frequently associated with various inflammatory states and may be increased in urticarial reactions, mastocytosis, and basophilia. Histamine also acts as a neurotransmitter in the central nervous system (CNS). Upon release from its storage sites, histamine exerts effects ranging from mild irritation and itching to anaphylactic shock and eventual death.

Histamine is found in animal tissues and venoms and in many bacteria and plants. Within the human body, the largest histamine concentrations are in the skin, lungs, and gastrointestinal mucosa, while concentrations are smaller in almost all other organs and tissues. Histamine is present in human plasma at relatively low concentrations (usually less than 0.5 ng/mL); in contrast, whole-blood levels can be as high as 30-fold greater. Substantial quantities of histamine are present in urine, with excretion rates varying from 10 to 40 μg per 24 hours.

Synthesis and Storage

Virtually all of the histamine found in individual organs and tissues is synthesized locally and stored in subcellular secretory granules. *Within the tissues, the mast cells are the principal sites of storage; in the blood, the ba-*

sophils serve this function. Histamine is also present in neurons of the CNS, where it acts as a neurotransmitter.

Histamine is synthesized from the amino acid histidine by an action of the enzyme *histidine decarboxylase* (Fig. 38.1). Following synthesis, histamine is either rapidly inactivated or stored in the secretory granules of mast cells and basophils as an inactive complex with proteases and heparin sulfate or chondroitin sulfate.

Release from Storage Sites

Histamine can be released from mast cell granules in two ways, both of which have pharmacological impor-

tance. Endogenous or exogenous compounds can promote an exocytotic release of histamine without cell destruction or lysis. Alternatively, histamine can be released from mast cells by a variety of nonexocytotic processes, including mast cell lysis, modification of mast cell membranes, and physical displacement of histamine.

Both *exocytotic* and *nonexocytotic* mechanisms can contribute to adverse drug reactions that involve histamine release. Histamine is only one of several potent physiological mediators that are released from mast cells; the other substances can also contribute to the overall immediate hypersensitivity reaction.
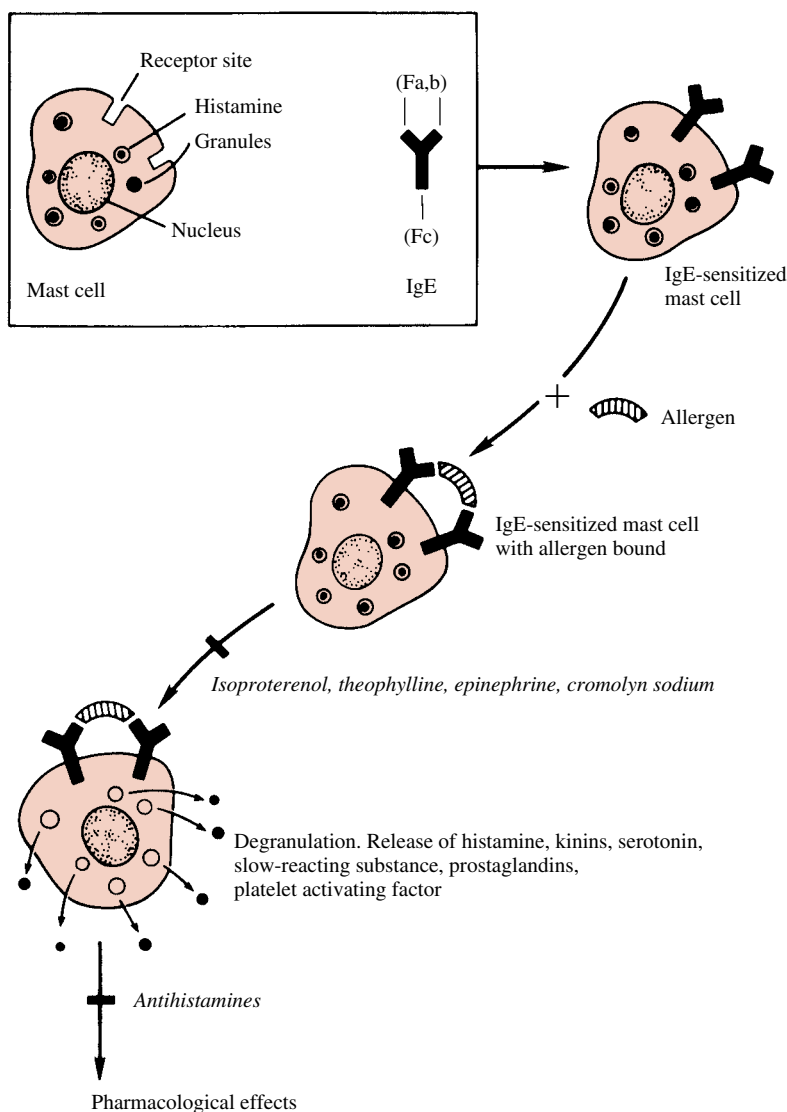
FIGURE 38.1

IgE-mediated release of mast cell contents. *Inset,* Intact mast cell with histamine stored in granules. An IgE antibody molecule is depicted adjacent to the mast cell. Two IgE molecules combine with a mast cell (sensitization). The attachment of an antigen (allergen) to the sensitized mast cell initiates release of histamine (and other substances) from the mast cell. This degranulation can be prevented by such agents as isoproterenol, theophylline, epinephrine, and cromolyn sodium. H_1 antihistamines do not interfere with degranulation but instead prevent actions of histamine at various pharmacological receptors.

Antigen-Mediated Histamine Release

Specific antigen–antibody interactions initiate the degranulation of tissue mast cells and blood basophils as part of the immediate hypersensitivity reaction. Immunoglobulin E (IgE) antibodies (reaginic antibodies) directed against an allergenic substance attach to the outer surface of the cell membrane and initiate a series of biochemical events that culminate in the release of the secretory granule contents (Fig. 38.1). Although allergens are the most frequent initiators of immediate hypersensitivity reactions, certain drugs, particularly in association with endogenous high-molecular-weight molecules, may also promote the sensitization process and mast cell degranulation on subsequent drug exposure.

Certain endogenous and exogenous compounds modulate the antigen-mediated release of histamine from sensitized tissues. Histamine inhibits its own release in skin mast cells and blood basophils by binding to H_2 histamine receptors, which when activated, inhibit degranulation. This feedback inhibition does not appear to occur in lung mast cells. Agonists of β_2-adrenoceptors inhibit antigen-induced histamine release from mast cells, whereas muscarinic and α-adrenergic agonists enhance mast cell degranulation.

Non–Antigen-Mediated Release of Histamine

Histamine may be released from mast cells by mechanisms that do not require prior sensitization of the immune system. Drugs, high-molecular-weight proteins, venoms, and other substances that damage or disrupt cell membranes can induce the release of histamine. Any thermal or mechanical stress of sufficient intensity also will result in histamine release. Cytotoxic compounds, may release histamine as the result of disruption of cell membranes.

Drugs, particularly organic bases, may release histamine from mast cells by physically displacing the amine from its storage sites. Morphine, codeine, *d*-tubocurarine, guanethidine, and radiocontrast media can release histamine from mast cells. Basic polypeptides, such as bradykinin, neurotensin, substance P, somatostatin, polymyxin B, and the anaphylatoxins resulting from complement activation, also stimulate histamine release. Venoms often contain basic polypeptides as well as the histamine-releasing enzyme phospholipase A.

Inactivation of Released Histamine

The inactivation of histamine is achieved both by enzymatic metabolism of the amine and by transport processes that reduce the concentration of the compound in the region of its receptors. Histamine metabolism occurs primarily through two pathways (Fig. 38.1). The most important of these involves *histamine N-methyltransferase*, which catalyzes the transfer of a methyl group from S-adenosyl-1-methionine to one of the imidazole nitrogen substitutions, forming 1-methylhistamine. This enzyme is present in tissues but not in blood. 1-Methylhistamine is converted by monoamine oxidase (MAO) to 1-methylimidazoleacetic acid.

An alternative pathway of histamine metabolism involves oxidative deamination by the enzyme *diamine oxidase* (*histaminase*) to form 5-imidazoleacetic acid. Diamine oxidase is present in both tissues and blood and plays a particular role in metabolizing the large concentrations of histamine that may be present in food. An additional metabolite, *N*-acetyl histamine (a conjugate of acetic acid and histamine), can be produced if histamine is ingested orally. This product may result from metabolism of histamine by gastrointestinal tract bacteria. Because of its rapid breakdown after oral administration, histamine produces few systemic effects when given by this route.

Physiological Effects of Histamine

Histamine mediates a diverse group of processes ranging from vasodilation to gastric acid secretion. It produces its effects by binding to and activating receptors on the surface of cardiac, smooth muscle, endothelial, neuronal, and other cells. There are at least four receptor populations, H_1, H_2, H_3, and H_4. All four receptor subtypes have been cloned and belong to the G protein–coupled receptor superfamily. The histamine receptors can be distinguished on the basis of their post–receptor signal transduction mechanisms, tissue distribution, and sensitivities to various agonists and antagonists (Table 38.1). Currently, only the H_1- and H_2-receptors are targets of clinical drug therapy.

Cardiovascular System

A slow intravenous injection of histamine produces marked vasodilation of the arterioles, capillaries, and venules. This causes a fall in blood pressure whose magnitude depends on the concentration of histamine injected, the degree of baroreceptor reflex compensation, and the extent of histamine-induced release of adrenal catecholamines. Vasodilation of cutaneous blood vessels reddens the skin of the face, while a throbbing headache can result from vasodilation of brain arterioles. Vasodilation is mediated through both H_1- and H_2-receptors on vascular smooth muscle. Stimulation of H_1-receptors produces a rapid and short-lived response, whereas stimulation of H_2-receptors produces a more sustained response that is slower in onset. Stimulation of H_3-receptors on sympathetic nerve terminals inhibits the release of norepinephrine and its associated vasoconstriction.

Histamine increases the permeability of capillaries and postcapillary vessels, resulting in passage of fluid

T A B L E 38.1   Histamine Receptors

Receptor	G Protein	Intracellular Signaling	Tissue Distribution	Selective Agonists	Selective Antagonists
H_1	$G_{q/11}$	Phospholipase C–mediated Ca^{++} mobilization	Brain, smooth muscle, heart, endothelium	2-(3-trifluoromethyl) phenyl histamine	Mepyramine, chlorpheniramine, triplodine
H_2	G_s	Adenylyl cyclase–catalyzed cAMP production	Brain, stomach, smooth muscle, heart, mast cells	Arpromidine, impromidine, amthamine, dimaprit	Cimetidine, ranitidine, famotidine
H_3	$G_{i/o}$	Decreased Ca^{++} influx through G protein–coupled N-type Ca^{++} channels	Brain, autonomic nerve endings, some endothelia	Imetit, immepip, R-α-methylhistamine	Thioperamide, iodophenpropit, clobenpropit
H_4	$G_{i/o}$	Decreased Ca^{++} influx through G protein coupled N-type Ca^{++} channels	Bone marrow, brain, peripheral leukocytes, lung	–	–

and protein into the extracellular space and eventually edema. This H_1-receptor–mediated process is responsible for the urticarial effect of histamine on the skin (hives).

In addition to its effects on the vasculature, histamine exerts direct positive inotropic and chronotropic effects on the heart through the stimulation of H_2-receptors. H_3-receptors on sympathetic nerve terminals in the heart decrease norepinephrine release; however, this effect appears to be significant only during stress states such as ischemia.

Extravascular Smooth Muscle

Histamine stimulates bronchiolar smooth muscle contraction through activation of H_1-receptors. A much smaller bronchodilatory response is evoked by stimulation of H_2-receptors. Asthmatics are generally more sensitive to the bronchoconstrictor actions of histamine than are nonasthmatics.

Histamine is able to cause uterine contraction. Although the magnitude of this effect in humans is normally small, the large amounts of histamine released during anaphylactic reactions can initiate abortion in pregnant women. Histamine can also stimulate contraction of gastrointestinal smooth muscle, with large doses able to produce diarrhea.

Glandular Tissue

Histamine stimulates the secretion of gastric acid and pepsin through an effect on the H_2-receptors of the parietal cells of the gastric mucosa. Secretion of acid is a complex process that is stimulated by histamine, acetylcholine, and gastrin and inhibited by somatostatin. The ability of H_2-receptor antagonists to inhibit the enhanced gastric acid secretion caused by acetylcholine and gastrin suggests that histamine release is of primary

importance in this process. Histamine also stimulates secretion by the salivary glands and glands in the small and large intestines. High concentrations of histamine promote the release of catecholamines from the adrenal gland.

Nervous System

Postsynaptic H_1- and H_2-receptors are responsible for a variety of processes in the CNS. H_1-receptors mediate the maintenance of wakeful states, while H_1- and H_2-receptors participate in the regulation of blood pressure, body temperature, fluid homeostasis, and pain sensation. Presynaptic H_3-receptors serve as feedback inhibitors of the release of histamine, norepinephrine, and other neurotransmitters.

In the periphery, H_1-receptors on sensory neurons in the epidermis and dermis mediate itch and pain, respectively. Autonomic afferent nerve endings may be similarly stimulated by histamine. As in the CNS, presynaptic H_3-receptors act in a feedback inhibitory capacity.

Lewis Triple Response

The *Lewis triple response* illustrates the effects of histamine on vascular smooth muscle, vascular endothelium, and sensory nerve endings. Intradermal injection of as little as 10 μg histamine produces three distinct effects:

1. Dilation of capillaries in the immediate vicinity of the injection results in a local red or blue region (*flush*).
2. Dilation of arterioles results in an irregular red *flare* over an area that is generally wider than that due to the capillary dilation. The flare probably results from an axon reflex in which histamine stimulates autonomic nerve endings, causing release of vasodilatory mediators.

3. Swelling (*wheal*) appears in the area of capillary dilation. The increased permeability of the blood vessels in this region is responsible for the edema.

In addition to the flush, wheal, and flare, transient pain and itching result from the effects of histamine on sensory nerve endings. In sensitized individuals, intradermal injection of specific antigens produces a wheal; this reaction is the basis for a skin test to quantify the extent of the allergic response.

Anaphylaxis

During an anaphylactic reaction, large quantities of inflammatory mediators are rapidly released. The resultant reaction is severe and may threaten the life of the individual. The introduction of a specific antigen—usually in food or in injected material—into a sensitized individual can cause the rapid release of mast cell contents, producing a decrease in blood pressure, impaired respiratory function, abdominal cramps, and urticaria. Extreme and severe anaphylaxis is life threatening and requires prompt medical intervention.

Clinical Uses of Histamine

Histamine has only minor uses in clinical medicine. In the past it was used to diagnose pernicious anemia, in which histamine fails to evoke the usual secretion of gastric acid. Histamine has been used to assess bronchial hyperreactivity, although this test may be quite hazardous for asthmatics. Today the main clinical use of histamine is as a positive control injection for allergy skin testing.

HISTAMINE ANTAGONISM AND HISTAMINE ANTAGONISTS

The effects of histamine on body tissues and organs can be diminished in four ways: inhibition of histamine synthesis, inhibition of histamine release from storage granules, blockade of histamine receptors, and physiological antagonism of histamine's effects. Of these approaches, only the inhibition of histamine synthesis has not been employed clinically. The focus of this chapter is on H_1 histamine receptor antagonists; it provides a brief overview of the H_2 blockers and the inhibitors of histamine release. More details can be found in Chapters 39 and 40.

H_1-Receptor Antagonists

The most common use of the H_1-receptor antagonists is for the relief of allergic reactions such as rhinitis and urticaria. These compounds are also used to prevent motion sickness, to treat vestibular disturbances, such as Ménière's syndrome, and as over-the-counter sleep aids.

Chemistry

The H_1-receptor antagonists for the most part are substituted ethylamine compounds. In comparison with histamine, the H_1-antagonists contain no imidazole ring and have substituents on the side chain amino group.

The H_1-antagonists are classified as either first- or second-generation compounds. Second-generation antihistamines have lipophilicity and ionization profiles that make them less able to cross the blood-brain barrier; thus they produce dramatically less sedation than do the first-generation drugs.

Pharmacokinetics

First-generation antihistamines are well absorbed after oral administration, with peak blood levels occurring within 1 to 2 hours; the therapeutic effect usually lasts 4 to 6 hours, although some drugs are much longer acting (Table 38.2). These antagonists are generally metabolized in the liver through hydroxylation. The metabolites and a small amount of parent compound are excreted in the urine.

The second-generation H_1-receptor antagonists are also rapidly absorbed, with peak plasma concentrations being reached within 1 to 3 hours. Their duration of action generally varies between 4 and 24 hours (Table 38.2). Loratadine (*Claritin*) and its active metabolite, desloratadine (*Clarinex*), undergoes extensive first-pass metabolism and is converted by CYP3A4 isozymes to an active metabolite. A number of drug interactions result from the ability of various compounds to induce, inhibit, or compete for metabolism by this cytochrome P450 system. In contrast, cetirizine (*Zyrtec*) and fexofenadine (*Allegra*) undergo little hepatic metabolism and are eliminated mainly as unchanged compounds in the urine and feces, respectively.

The reduction in therapeutic effectiveness that can occur when antihistamines are given for long periods is probably related to an induction of hepatic drug-metabolizing enzymes. Children tend to eliminate antihistamines more rapidly than adults, while individuals with hepatic impairment may eliminate them more slowly.

Mechanism of Action

At therapeutic doses, the first- and second-generation antihistamines are equilibrium-competitive inhibitors of H_1-receptor–mediated responses. Certain second-generation drugs are noncompetitive inhibitors at high concentrations. Both first- and second-generation compounds have negligible abilities to block the H_2-, H_3-, or H_4-receptors. The therapeutic effectiveness of these

TABLE 38.2 Representative H$_1$Receptor Antagonists

Drug	Trade Name	Duration of Action (hr)	Sedative Activity	Anti–Motion Sickness Activity	Anticholinergic Activity
First-Generation Antihistamines					
Ethanolamines					
Carbinoxamine	Rondec	3–6	++		+++
Clemastine	Tavist	12	++		+++
Diphenhydramine	Benadryl	4–6	+++	++	+++
Dimenhydrinate	Dramamine	4–6	+++	++	+++
Ethylenediamines					
Pyrilamine	Ryna	4–6	++		+
Tripelennamine	PBZ	4–6	++		+
Alkylamines					
Chlorpheniramine	Chlor-Trimeton	4–6	+		+
Brompheniramine	Dimetane	4–6	+		+
Piperazines					
Cyclizine	Marezine	4–6	+	++	++
Hydroxyzine	Atarax		+++	+++	+++
Meclizine	Antivert	12–24	+	++	++
Phenothiazines					
Promethazine	Phenergan	4–6	+++	+++	+++
Piperidines					
Cyproheptadine	Periactin	4–6	++		++
Second-Generation Antihistamines					
Piperidines					
Loratadine	Claritin	24			
Fexofenadine	Allegra	12			
Piperazines					
Cetirizine	Zyrtec	12–24			

+, slight activity, ++, moderate activity, +++, marked activity

drugs arises from their capacity to block histamine-mediated vasoconstriction, microvascular permeability enhancement, and sensory nerve terminal stimulation. H$_1$-antagonists generally produce sedation through an effect on the CNS; however, excitation can occur when toxic dosages are ingested.

Many of these drugs have effects that are not mediated by H$_1$-receptors (Table 38.2). The antimuscarinic activity of several first-generation H$_1$-blockers may account for their effectiveness in combating motion sickness and their limited ability to suppress parkinsonian symptoms. The phenothiazines have some capacity to block α-adrenoceptors, whereas cyproheptadine (*Periactin*) is an antagonist at serotonin receptors. Diphenhydramine (*Benadryl*), pyrilamine (*Ryna*), and promethazine (*Phenergan*) are effective local anesthetics. Many second-generation antihistamines also have been found to inhibit the non–histamine-mediated release of various inflammatory substances; this may account for some of their effectiveness in allergic conditions.

Adverse Effects

Sedation is the most frequent adverse reaction to the first-generation antihistamines. An additive effect on alertness and motor skills will result if alcohol or another depressant is taken with these drugs. Antimuscarinic effects caused by these drugs include dry mouth and respiratory passages, urinary retention, and dysuria. Nausea, vomiting, constipation or diarrhea, dizziness, insomnia, nervousness, and fatigue also have been reported. Drug allergy, especially after topical application, is fairly common. Tolerance to certain antihistamines may develop after prolonged administration. Teratogenic effects of the piperazine antihistamines have been shown in animal studies. Epidemiological

studies have not shown such an association in humans. The effects of toxic doses of first-generation antihistamines, similar to those seen following atropine administration, include excitement, hallucinations, dry mouth, dilated pupils, flushing, convulsions, urinary retention, sinus tachycardia, coma, and death.

The second-generation H_1-antagonists are often referred to as nonsedating antihistamines; however, doses above the usual therapeutic level can cause sleepiness in certain individuals. A more serious adverse effect of some earlier second-generation antihistamines is cardiotoxicity. Terfenadine (*Seldane*) and astemizole (*Hismanal*) were withdrawn from the U. S. market after they were found, in rare cases, to induce a potentially fatal ventricular arrhythmia, *torsades de pointes*. These drugs block the cardiac K^+ channels responsible for the repolarizing current (I_{Kr}) of the action potential (see Chapter 16) and therefore prolong the QT interval. Arrhythmias result when these drugs accumulate to toxic levels, such as when their metabolism is impaired, as in liver disease or following coadministration of drugs that inhibit the CYP3A family of enzymes. Fexofenadine, the active antihistaminic metabolite of terfenadine, does not produce *torsades de pointes*.

Clinical Uses

The H_1-receptor blocking drugs find their greatest use in the symptomatic treatment of allergic conditions. The second-generation antihistamines and the first-generation alkylamines are most frequently used to treat allergic rhinitis. Allergic conjunctivitis and the acute form of urticaria are also effectively treated with antihistamines. The allergic responses seen in susceptible individuals after intradermal injections of allergens (e.g., skin testing) can be prevented for several hours by prior administration of H_1-antagonists. However, the H_1-antagonists are not drugs of choice in acute anaphylactic emergencies or the viral-caused common cold.

Although the antihistamines are not useful as primary agents in the treatment of asthma, a number of studies have shown that the second-generation compounds are effective as adjunctive therapies in asthmatic patients with concomitant rhinitis, urticaria, or dermatitis. Cetirizine has been used to prevent the progression from atopic dermatitis to asthma in young children.

Another important use of H_1-antagonists is in the treatment of motion sickness. Diphenhydramine (*Benadryl*), dimenhydrinate (*Dramamine*), cyclizine (*Marezine*), and meclizine (*Antivert*) have anticholinergic activity and are the preferred antihistaminic agents for reducing the symptoms of motion sickness.

Diphenhydramine is known to be at least partially effective in Parkinson's disease, perhaps because of its anticholinergic properties.

Many H_1-receptor blocking drugs have sedative properties, and some have been used in over-the-counter sleep aids. The most widely used H_1-blocking drugs for sleep induction are diphenhydramine, promethazine, and pyrilamine.

H_2-Receptor Antagonists

The H_2-receptor blockers include cimetidine, famotidine, and ranitidine. These drugs are used to decrease gastric acid secretion in the treatment of peptic ulcer, gastroesophageal reflux disorder, and hypersecretory conditions, such as Zollinger-Ellison syndrome. The pharmacodynamics and clinical uses of these drugs are discussed in Chapter 40.

Cromolyn and Nedocromil

Although cromolyn sodium (*Intal*) and nedocromil sodium (*Tilade*) are widely known for their ability to prevent the release of histamine and other inflammatory mediators by mast cells during the early response to antigen challenge, these drugs have a wide variety of inhibitory effects on many cell types, including eosinophils, neutrophils, monocytes, and neurons. Cromolyn sodium and nedocromil sodium are used as pulmonary inhalants in the treatment of asthma. Nasal (*Nasalcrom*) and ophthalmic (*Opticrom*) preparations of cromolyn sodium can be used to reduce the symptoms of allergic rhinitis and conjunctivitis. More detailed information on these compounds may be found in Chapter 39.

New Directions in Antihistamine Therapy

None of the selective agonists and antagonists of H_3-receptors are available for clinical use. Antagonists of H_3-mediated inhibition of neurotransmission may have potential in the treatment of CNS disorders, since animal studies have found that these compounds may enhance learning, ameliorate learning deficits, and decrease seizure activity. H_3-receptor agonists have been shown to inhibit gastric acid release and block certain inflammatory processes. In cardiac ischemia, they can prevent the arrhythmia and cardiac damage that may result from norepinephrine overflow and thus may be useful in the treatment of myocardial infarction. Selective agonists and antagonists of H_4-receptors are not yet available.

Study QUESTIONS

1. The antigen-mediated release of histamine can
   (A) Be inhibited by the binding of histamine to H_3-receptors on mast cells
   (B) Be stimulated by β_2-adrenoceptor agonists
   (C) Be initiated by organic bases such as morphine without prior sensitization
   (D) Occur only in the tissues, not in the blood
   (E) Produce pain and itching through an effect on sensory nerve endings

2. Effects mediated by the H_1 histamine receptor include
   (A) Inhibition of gastric acid secretion
   (B) Induction of hepatic cytochrome P450 enzymes
   (C) Maintenance of a wakeful state
   (D) Bronchodilation
   (E) Vasoconstriction of arterioles

3. All four types of histamine receptors
   (A) Are found on the surface of mast cells and basophils
   (B) Are G protein–coupled
   (C) Modulate adenylyl cyclase activity
   (D) Are involved in the release of multiple neurotransmitters

4. Ms. Jones takes fexofenadine 60 mg twice a day for seasonal allergies. She comes to her physician with a sinus infection and receives a prescription for erythromycin, a drug known to inhibit CYP3A4. As a result of this drug interaction, you would expect Ms. Jones to
   (A) Exhibit no changes in fexofenadine elimination
   (B) Exhibit decreased metabolism of erythromycin, with potential toxicity
   (C) Be at risk for development of torsades de pointes, due to decreased metabolism of fexofenadine
   (D) Exhibit decreased elimination of fexofenadine without risk of torsades de pointes
   (E) Exhibit moderate anticholinergic effects commonly seen with fexofenadine

5. Mr. Smith has severe motion sickness during air travel. He will be flying to Brazil next week, and you, his physician, would like to prescribe an antihistamine to prevent motion sickness. Which of the following would be most effective?
   (A) Scopolamine
   (B) Dimenhydrinate
   (C) Chlorpheniramine
   (D) Fexofenadine
   (E) Tripelennamine

ANSWERS

1. **E.** Histamine inhibits its own release through an effect on H_2-receptors on mast cells. Its release is inhibited, not stimulated, by β_2-adrenoceptor agonists. Organic bases can displace histamine from its storage granules and cause non–antigen-mediated release of histamine; antigen-mediated release requires prior sensitization. Antigen-mediated histamine release occurs in both tissues and blood. Histamine stimulates sensory nerve endings, resulting in pain and itching.

2. **C.** Histamine stimulates gastric acid secretion through an effect on H_2-receptors of gastric parietal cells. Although certain antihistamines are metabolized by cytochrome P450 enzymes, histamine does not induce their production. Histamine helps to maintain a wakeful state through an effect on H_1-receptors. Histamine-mediated broncho*constriction* is mediated by H_1-receptors, while histamine-mediated vaso*dilation* occurs as a result of stimulation of H_1- and H_2-receptors.

3. **B.** H_2-receptors are found on the surface of mast cells and basophils. All four types of histamine receptors belong to the G protein–coupled receptor superfamily. Only H_2-receptors are coupled to adenylyl cyclase through the G protein G_s.

4. **A.** Fexofenadine undergoes little or no hepatic metabolism and is excreted primarily as unchanged drug. Therefore, administering an inhibitor of CYP3A4 would not affect fexofenadine elimination. Fexofenadine does not inhibit erythromycin metabolism, nor does it produce *torsades de pointes*. Unlike many first-generation antihistamines, fexofenadine does not have anticholinergic side effects.

5. **B.** Although scopolamine effectively combats motion sickness, it is an antimuscarinic agent, not an antihistamine. Dimenhydrinate is an antihistamine with significant antimuscarinic properties that are likely to contribute to its anti–motion sickness activity. Chlorpheniramine, fexofenadine, and tripelennamine are antihistamines without significant efficacy in the treatment of motion sickness.

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C A S E Study Behavior Changes and the Bladder

Anisette Doe, a 28-year old woman, went to the emergency department with abdominal bloating and inability to void her bladder; she had been unable to urinate for 16 hours. A urinary catheter was inserted and 2.5 L of urine was withdrawn. Subsequent testing revealed no calculi or masses in the bladder, urethra, ureters, or kidneys. Ms. Doe's medical records indicated that she was being treated with clozapine for paranoid schizophrenia. She reported no significant side effects as a result of this treatment. For 2 days prior to admission to the hospital, Ms. Doe complained of a cold and was taking diphenhydramine (*Benadryl*) 50 mg every 6 to 8 hours. What is a possible explanation for the sudden onset of her inability to void her bladder?

The case in context: Clozapine is a newer antipsychotic that can, like other agents in its class, produce antimuscarinic side effects. Although Ms. Doe had not complained of anticholinergic effects prior to beginning treatment with a moderate dose of diphenhydramine, it is likely that the additive anticholinergic effects of clozapine and diphenhydramine resulted in urinary retention.