Autocoids

- Dr.Gowhar ali

University of Peshawar

Autacoids

Definition: Auto = self Coids = Remedy

or some times called Local Hormones

Autacoids are biological factors which act like local hormones, have a brief duration, act near the site of synthesis, and are not blood borne. The word autacoids comes from the Greek "Autos" (self) and "Acos" (relief, i.e. drug). These are local hormones and therefore have a paracrine effect.

play an important role

in the physiological and

pathological processes;

- They take part in:
  1. Inflammation
  2. Allergic reactions
  3. Anaphylactic reactions(not so much)
  4. Neurotransmission
  5. Gastric acid secretion
  6. Neuroendocrine regulation
- In the central nervous system, they are responsible for
  1. Wakefulness
  2. Decreased Appetite
  3. Regulation of drinking
  4. Regulation of temperature
  5. Secretion of ADH
  6. Control of blood pressure
  7. Perception of pain.

Classification:

1.Amines

1.Histamine

2.5-hydroxytryptamine (Serotonin)

2.Polypeptides:

A. Vasoconstrictors:

Angiotensin II

Endothelin

Vasopressin

Neuropeptide Y

B. Vasodilators:

Kinins

Vasoactive intestinal polypeptides

Substance P

Neurotensin

Calcitonin-gene related peptide (CGRP)

C. Miscellaneous:

Cytokines

3.Lipid soluble organic acids:

A. Ecosanoids:

1.Leukotrienes

2.Protaglandins

Histamine & Antihistaminic Drugs:

Histamine:

- Def: Autocoids
  biogenic amines
- Source: : plants and animals including humans
  . present in stinging secretion of
  . wasps, scorpions etc. and venoms.
  . In skin, Lungs, G.I.T, mucosa, Blood (basophils)
- Synthesis: Biosynthesis is from decarboxylation of histidine
  Serotonin is made from tryptophan.
- Storage: In mast cells, vesicles, which are present in Lungs, mucosa, skin etc...
- Release: Immunologic Release/allergic reactions: from already sensitized basophils.

21 Monday

b) Mechanical and chemical release. may be due to injury of drug eg D-Tubocurarine, morphine.

Mechanism of Action:

Histamine acts on histaminergic receptors H_1, H_2, H_3, H_4. These are G protein coupled receptors.

H_1: $\xrightarrow{Gq}$ IP_3 + DAG (vascular cell/endothelium)

H_2: —— gastric parietal cells. $\xrightarrow{H_2}$ $\xrightarrow{G_s}$ $\xrightarrow{}$ cAMP ↑↑↑

H_3: different parts of Brain. $\xrightarrow{H_3}$ $\xrightarrow{Gi}$ $\xrightarrow{}$ cAMP ↓↓

H_1 Blockers:

Classification:

① 1st generation/conventional/classical/old:

② 2nd generation/latest/new drugs

1st generation drugs pharmacokinetics:

These are sedative in nature, psychomotor performance are distrubed, with-drawl is necessary.

1st generation drugs can cross the blood brain barrier and can cause sedative hypnotic.

2nd generation drugs cannot cross the BBB or slightly cross the BBB, so there is no or very slight sedation.

But 2nd generation drugs are relatively expensive.

1st generation Drugs classifications:

according to chemistry

a) Ethanol amine derivaitives:

Dimenhydrinate (Gravinate®)

- Diphenhydramine (Benadryl®)
- Doxylamine
- Brompheniramine
- Carbinoxamine

② **Ethylene diamine derivaitives:**
- Pyrilamine
- Tripelennamine

③ **Piperazine derivaitives:** Hydroxazine (Atarax®)
- Meclizine, Buclizine
- Cyclizine, Chlorizine

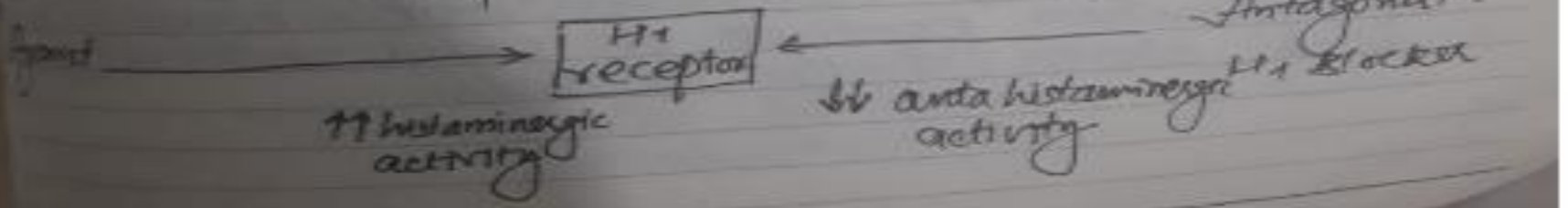
④ **Alkyl amine derivaitives:**
- Brompheniramine Malate
- Chlorpheniramine Malate (Piriton® Avil®)
- Doxpheniramine malate
- Triprolidine (Actidil)

⑤ **Phenothiazine derivaitives:**
- Promethazine (Phenargan®)
- Isomethazine

2nd generation Antihistaminic Drugs:

Cetrizine (Risek®)/Zyrtec®
Levocetrizine
Loratidine, Fexofenadine (Telfast®/Forcet®)
Terfenadine: banned due to causation of cardiac arrhythmias.
Astemizole: Banned in 1998-99
Mizolastine; Ebastine, Azelastine, Mezolastine

Pharmacodynamics:
Competative Pharmacological antagonism.



July

23 Wednesday

Clinical Uses:

① Allergic reactions / hypersensitivity reactions of different organs including rhinorrhea, conjunctivitis, itching, pruritis, urticaria, eye drops, common colds, flu like conditions.
Blood transfusion reaction.

② Pre anesthetic medications:
Promethazine, diphenhydramine.

③ Anti emetic properties: (motion sickness)
dimenhydrinate, promethazine

④ Anti parkinsonism therapy.
due to anticholinergic activity.

⑤ Anti-vertigo therapy:
ménière's disease.

Side effects:

1st generation:

① most common side effects: Sedation / drowsiness
Lack of concentration, psychomotor performance are disturbed, fatigue / lassitude
Headache, weakness.

② These effects are not common with 2nd generation drugs

GIT:
epigastric pain, Anorexia.
Anticholinergic effect: Xerostomia.
Blurred vision, urinary retention,
Constipation
Teratogenic effects, defects by birth in foetus.

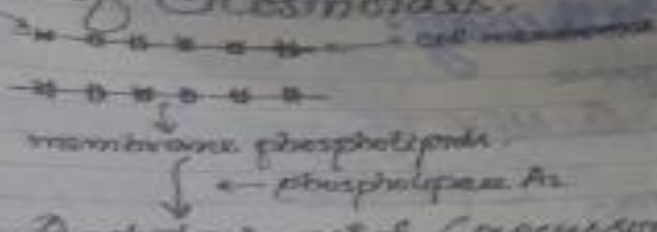
Prostaglandin's Pharmacology:

Eicosinoides:

Oxygenation 20 carboned double bonded compound
long chain products of polyunsaturated fatty acids.

Thursday 24

Biosynthesis of Eicosinoids:



Arachidonic acid (precursor compound)

Arachidonic Acid

- Cyclooxygenase pathway (PG Synthesis Pathway)
- Lipoxygenase pathway (LOX)
- Epoxide pathway → epoxides
- Free Radical pathway → free radical

Cox pathway:

Cox I → cytoprotective
Cox II → Inflammatory.

Cox II: → P.G H_2 → P.G G_2 → P.G D_2 (Bronchoconstrictor)

P.G I_2 → Thromboxane A_2

Thromboxane A_2: P.A, B.P, pain sensitization, vasodilatation

P.G I_2: Antiplatelet, cytoprotective

P.G E_2: uterine contraction, Cervical dilating, pain sensitization, fever.

P.G $E_2\alpha$:
- ↑ drainage of aqueous humor
- uterine contraction
- Bronchoconstrictor.

Lox Pathway:

5-lipoxygenase → 5-HPETE → 5-HETE → LTA_4 → LTB_4 (E)

LTA_4 (E) → LTC_4 → LTD_4 → LTE_4 ← Reconversion

S.A.I.Ds: → Annexins / Lipocortins (⊖)

S.A.I.Ds inhibits the Cox pathway (P.G.S.P) and ↓ P.G level which are involved in pain, Inflammation and pyrexia.

Phospholipase A2 (⊖ blocks) → arachidonic Acid synthesis → eicosinoids

N.S.A.I.Ds: (⊖) → Cox II enzyme.

Lox pathway

Zileuton (⊖) → | ← 5 Lox

→ LT

LT receptor antagonist: $[A_4, B_4, C_4, D_4, E_4]$

Zafirlukast (⊖)

Synthetic P.G.	Formulations	Clinical Uses
1. Dinoprostone (PGE_2)	Vaginal Tab + Gel	Induction of labour, Abortifacient, Mid term abortion
2. Dinoprost ($PGF_{2\alpha}$)	Intra Amniotic Inj	
3. Carboprost (15-methyl $PGF_{2\alpha}$)	IM, Intra Amniotic Inj	Post Partum Hemorrhage, M.T.A.
4. Gemeprost (PGE_1)	Vaginal Tab	Cervical priming (ripening) to Accelerate Labour.
5. Alprostadil	IV inf^{n}/Intra Cavernosal Inj	To maintain patency of ductus arteriosus. Erectile dysfunction.
6. Misoprostol (PGE_1)	oral, capsule	peptic ulcer
7. Epoprostenol (PGI_2)	IV inj	hypertension
8. Latanoprost ($PGF_{2\alpha}$)	Eye drops	Glaucoma, drainage of aqueous humor

Clinical Importance of Serotonin agonists & antagonists:

Serotonin:

Autocoid / Biologically active amine

Occurance: Brain, G.I.T., Blood, (Platelets)

Biosynthesis: Tryptophan ----> 5 hydroxy Tryptamine (5 HT) & neurotransmitter

Controls: Apetite, Sleep, Mood

Serotonin

Side two many receptors
5-HT1 5-HT2 5-HT3 5-HT4 5-HT5 5-HT6 5-HT7
5-HT1A 5-HT1B

Serotonin Agonists:

① As anti Anxiety drugs/ anxiolytics.

Buspirone : 5-HT1A Agonist
Non Benzodiazepine.

② Anti-Migrain Therapy:

Serotonin Agonist → 5-HT1B/5-HT1D receptor Agonist
Triptan drugs
Sumatriptan
Almo "
Ele "
Riza "
Zolmi "
Nara "
Frova "

Acute attacks ✓

③ Rx of obesity:

↑ release of serotonin
suppress appetite

Fenfluramine, Dexfenfluramine, Sibutramine.

④ GERD: gastro-esophageal reflux disease.

Benzapride
Cisapride 5-HT4 Agonist.

⑤ Rx of Depression: (Anti depressants) (SSRIs)
↑ the level of serotonin.

Fluoxetine
Citalopram
Escitalopram
Flavoxamine
Sertraline

⑥ 5-HT3 Receptor Antagonist (Antiemetics)

Ondansetrone
Granni "
Tropi "
Dola "
Alosetrone

G.T.I.V chemotherapy
R.T.I.V radiation
P.S.V per surgical

⑦ 5-HT2 Blockers:

Cyproheptadine → Carcinoid tumor

⑧ Kofa syrup

Reta syrup → Hiccup

3.Thrombaxanes

B. Platelet activating factor

Note:

Histamine inhibits its own release in skin mast cells and blood basophils by binding to H2 histamine receptors, which when activated, inhibit degranulation. This feedback inhibition does not appear to occur in lung mast cells. Agonists of Beta 2-adrenoceptors inhibit antigen-induced histamine release from mast cells, whereas muscarinic and alpha adrenergic agonists enhance mast cell degranulation.

Histamine

Histamine is found in animal tissues and venoms (Bees) and in many bacteria and plants. Within the human body, the largest histamine concentrations are found in areas exposed to external environment such as in the skin, lungs, and gastrointestinal mucosa, Basophils while concentrations are smaller in almost all other organs and tissues.

Synthesis

Histamine is synthesized from the amino acid histidine by an action of the enzyme histidine decarboxylase.

Release of histamine:

In common with many secretory processes, histamine release is initiated by a rise in cytosolic Ca2+. Various basic drugs, such as morphine and tubocurarine, release histamine through a non-receptor action. Agents that increase cAMP formation (e.g. β-adrenoceptor agonists) inhibit histamine secretion.

1. Physical and Chemical stimuli:

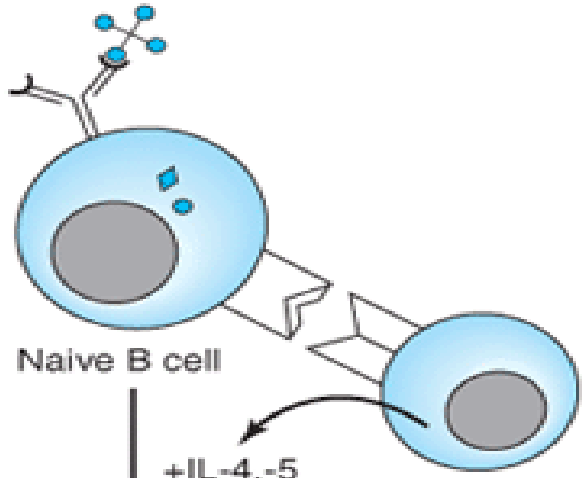
Heat, Cold, X rays,Detergents etc.

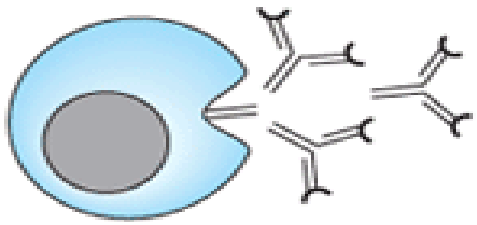
2. Antigen-Antibody reaction (Type 1 hypersensitivity reactions)

In this case IgE antibodies become attached to mast cell membrane and cause the release of histamine.

This image cannot currently be displayed.

Sensitization phase

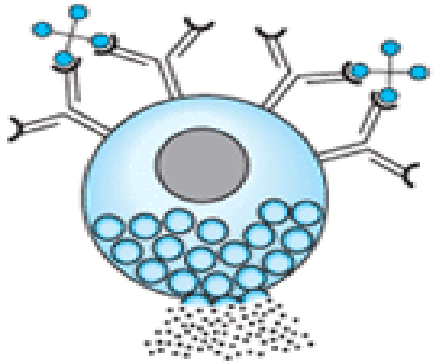




IgE-secreting plasma cell
IgE is specific for allergen

IgE binds IgE Fc receptors on mast cells or basophils

Effector phase



Allergen cross-links IgE on mast cell (or basophil) and triggers degranulation and release of pharmacologic mediators

Mediators
- Histamine
- Serotonin
- Leukotrienes
- Prostaglandins
- Bradykinins
- Proteases
- Eosinophil chemotactic factor
- Neutrophil chemotactic factor

→

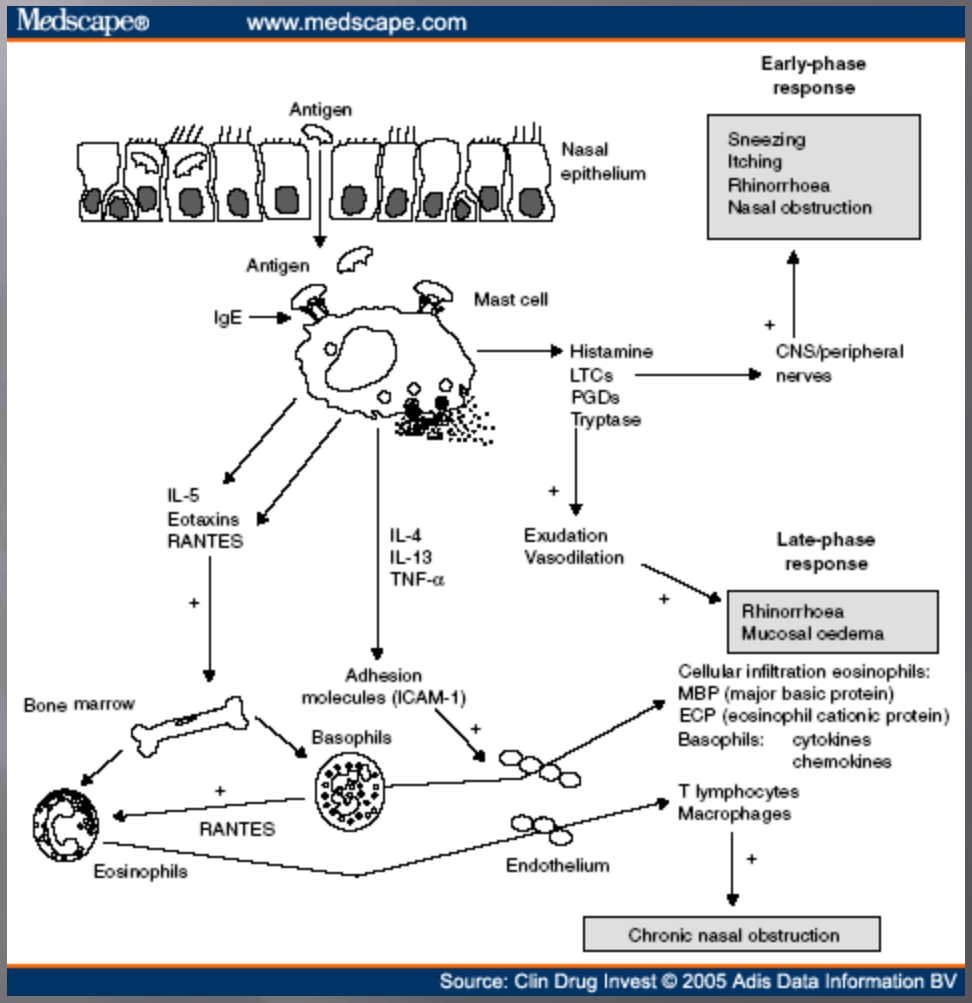
Effects
- Smooth muscle contraction
- Vasodilation
- Increased vascular permeability
- Platelet aggregation
- Complement activation
- Mucus secretion

→

Clinical symptoms
- Asthma
- Hay fever
- Skin rashes
- Local anaphylaxis
- Systemic anaphylaxis

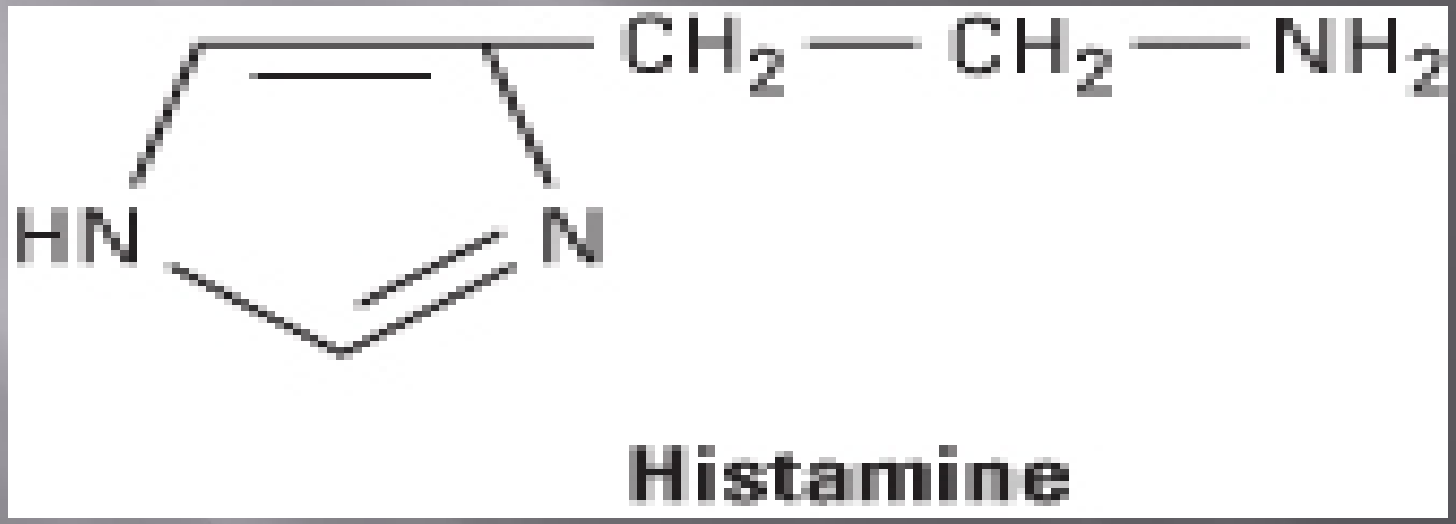
Figure:

Mechanism of type I hypersensitivity. Initial exposure to allergen (sensitization phase) leads to production of IgE by plasma cells differentiated from allergen-specific B cells (not shown). The secreted IgE binds IgE-specific receptors (FceR) on blood basophils and tissue mast cells. Reexposure to allergen leads to cross-linking of membrane-bound IgE (effector phase). This cross-linking causes degranulation of cytoplasmic granules and release of mediators that induce vasodilation, smooth muscle contraction, and increased vascular permeability. These effects lead to the clinical symptoms characteristic of type I hypersensitivity.


Medscape®
www.medscape.com
Early-phase response
Antigen
Nasal epithelium
Sneezing
Itching
Rhinorrhoea
Nasal obstruction
Antigen
IgE
Mast cell
Histamine
LTCs
PGDs
Tryptase
+
CNS/peripheral nerves
IL-5
Eotaxins
RANTES
IL-4
IL-13
TNF-α
Exudation
Vasodilation
Late-phase response
Rhinorrhoea
Mucosal oedema
Bone marrow
Adhesion molecules (ICAM-1)
Cellular infiltration eosinophils:
MBP (major basic protein)
ECP (eosinophil cationic protein)
Basophils: cytokines
chemokines
Basophils
RANTES
T lymphocytes
Macrophages
Eosinophils
Endothelium
Chronic nasal obstruction
Source: Clin Drug Invest © 2005 Adis Data Information BV

3.Drugs

Morphine, Codeine, D-tubacurarine, Trimetaphan etc



Histamine

Mechanism Of Action

Histamine exerts its biologic actions by combining with specific cellular receptors located on the surface membrane. The four different histamine receptors are designated H1-H4. All histamine are G protein coupled receptors.

1. H1 Receptors:

Activation of H1 receptors, which are present in endothelium, smooth muscle cells, and nerve endings, usually elicits an increase in IP3 and DAG and an increase in intracellular calcium.

2. H2 receptors

Activation of H2 receptors, present in gastric mucosa, cardiac muscle cells, and some immune cells, increases intracellular cyclic adenosine monophosphate (cAMP) via Gs. Like the Beta2 adrenoceptor, under certain circumstances the H2 receptor may couple to Gq, activating the IP3-DAG (inositol 1,4,5-trisphosphate-diacylglycerol) cascade.

3. H3 receptors

Activation of H3 receptors decreases transmitter release from histaminergic and other neurons,

probably mediated by a decrease in calcium influx through N-type calcium channels in nerve endings. These are Gi coupled receptors.

4. H4 receptors

H4 receptors are mainly found on leukocytes in the bone marrow and circulating blood.

Physiological Effects of Histamine

1. Bronchiolar smooth muscle;

In both humans, histamine causes bronchoconstriction mediated by H1 receptors.

2. Gastrointestinal tract smooth muscle

Histamine causes contraction of intestinal smooth muscle, and histamine-induced contraction of guinea pig ileum is a standard bioassay for this amine. The human gut is not as sensitive as that of the guinea pig, but large doses of histamine may cause diarrhea, partly as a result of this effect. This action of histamine is mediated by H1 receptors.

3. Other smooth muscle organs;

In humans, histamine generally has insignificant effects on the smooth muscle of the eye and genitourinary tract. However, pregnant women suffering anaphylactic reactions may abort as a result of histamine-induced contractions.

4. Nervous system

1. Nervous System Postsynaptic H1- and H2-receptors are responsible for a variety of processes in the CNS. H1-receptors mediate the maintenance of wakeful states. Presynaptic H3-receptors serve as feedback

inhibitors of the release of histamine, norepinephrine, and other neurotransmitters.

2. Histamine is a powerful stimulant of sensory nerve endings, especially those mediating pain and itching mediated by H1 receptors.

5. Cardiovascular System

In humans, injection or infusion of histamine causes a decrease in systolic and diastolic blood pressure and an increase in heart rate. The blood pressure changes are caused by the direct vasodilator action of histamine on arterioles and precapillary sphincters; the increase in heart rate involves both stimulatory actions

of histamine on the heart and a reflex tachycardia. Flushing, a sense of warmth, and headache may also occur during histamine administration, consistent with the vasodilation. Vasodilation elicited by small doses of histamine is caused by H1-receptor activation and is mediated primarily by release of nitric oxide from the endothelium. The decrease in blood pressure is usually accompanied by a reflex tachycardia. Higher doses of histamine activate the H2-mediated cAMP process of vasodilation and direct cardiac stimulation. In humans, the cardiovascular effects of small doses of histamine

can usually be antagonized by H1-receptor antagonists alone.

Histamine-induced edema results from the action of the amine on H1 receptors in the vessels of the microcirculation, especially the postcapillary vessels. The effect is associated with the separation of the endothelial cells, which permits the transudation of fluid and molecules as large as small proteins into the perivascular tissue. This effect is responsible for the urticaria (hives) that signals the release of histamine in the skin. Studies of endothelial cells suggest that actin and myosin within these cells contract, resulting in

separation of the endothelial cells and increased permeability.

There is positive ionotropic and chronotropic effects which is due to stimulation of H2 receptors in the heart and also reflexly due to fall in blood pressure.

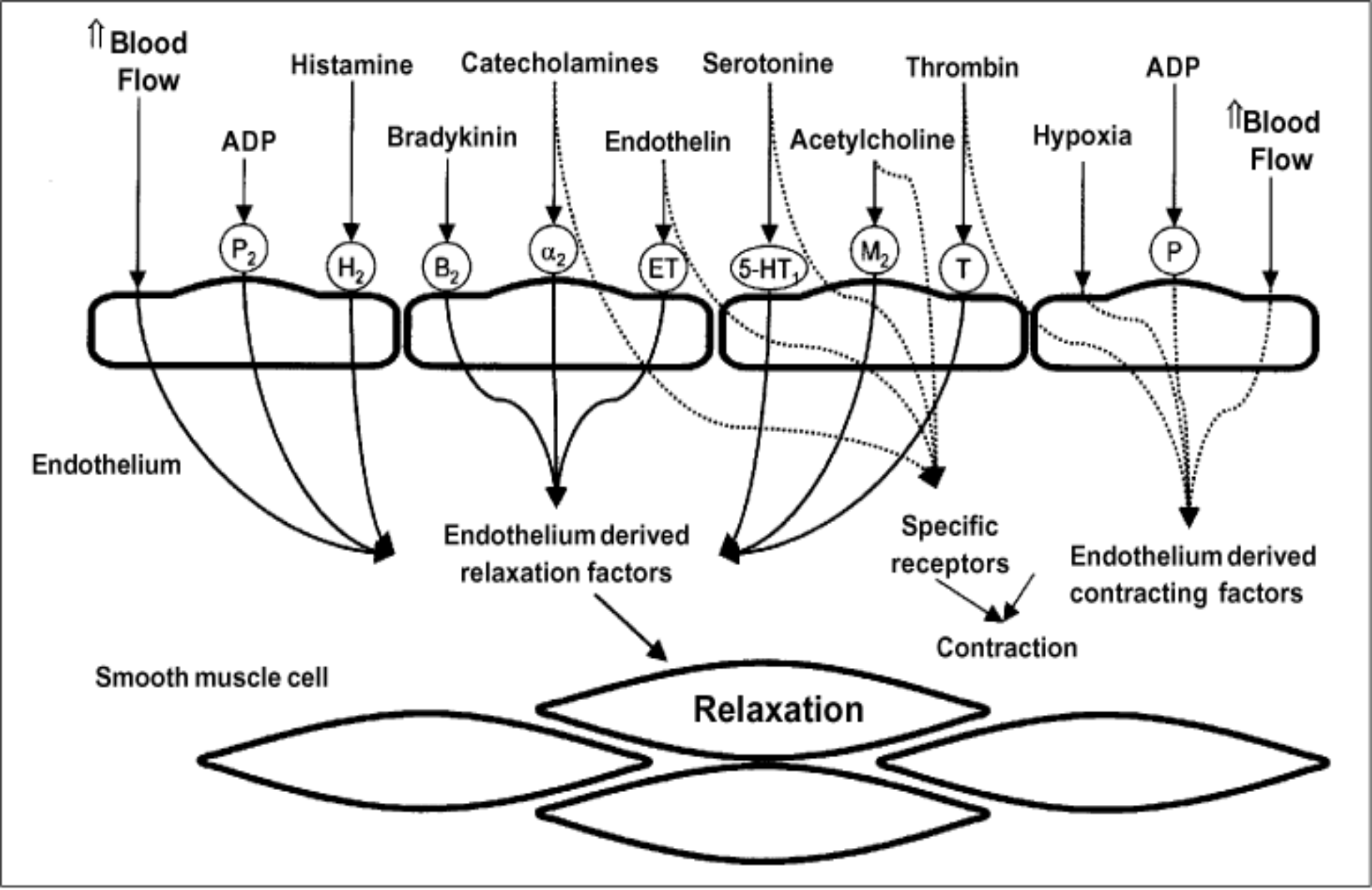


Fig. 1 – Diagram describing the action of various effectors on functionally intact endothelium. Receptor stimulation or direct action of these agents led to the liberation of endothelium-derived relaxation factors (nitric oxide, prostacyclin) that cause vascular smooth muscle cells to dilate. In contrast, serotonin, catecholamines, endothelin, acetylcholine, thrombin, hypoxia, adenosine diphosphate (ADP), and the stress of shearing (blood flow) may cause contraction of vascular smooth muscle cells. In functionally intact endothelium, vasodilatation predominates (H2- histamine receptor, a2- a-adrenergic receptor; 5-HT- serotoninergic receptor; B- bradykinin receptor; M- muscarinic receptor; P- purinergic receptor; ET- endothelin receptor; T- thrombin receptor).

6. 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 g 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.

7. Secretory tissue;

Histamine has long been recognized as a powerful stimulant of gastric acid secretion and, to a lesser extent, of gastric pepsin and intrinsic factor production. The effect is caused by activation of H2 receptors on gastric parietal cells and is associated with increased adenylyl cyclase activity, cAMP concentration, and intracellular Ca2+ concentration.

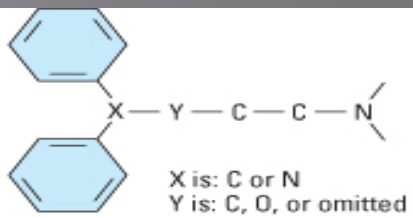
Type 1, anaphylactic reaction

Type 1, anaphylactic reaction is a drug-specific antibodies of the IgE type combine with receptors on the surface of mast cells or basophils. Binding of the drug provides the stimulus for the release of histamine and other mediators. In the most severe form, a lifethreatening anaphylactic shock develops, accompanied by hypotension, bronchospasm (asthma attack), laryngeal edema, urticaria, stimulation of gut musculature, and spontaneous bowel movements.

This image cannot currently be displayed.

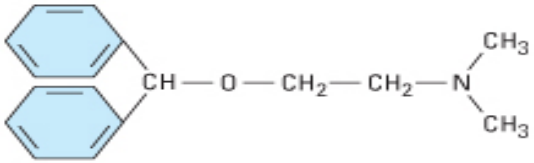
H1 receptor antagonists

The H1 antagonists are conveniently divided into first-generation and second-generation agents. These groups are distinguished by the relatively strong sedative effects of most of the first-generation drugs. The relatively less sedating characteristic of the second-generation H1 blockers is due in part to their less complete distribution into the central nervous system. All of the H1 antagonists are stable amines.



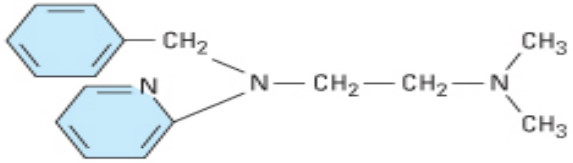
GENERAL STRUCTURE

ETHERS OR ETHANOLAMINE DERIVATIVE



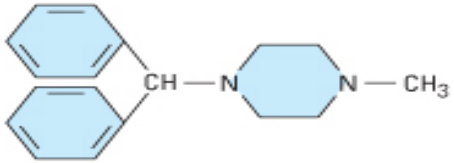
Diphenhydramine or dimenhydrinate

ETHYLENEDIAMINE DERIVATIVE



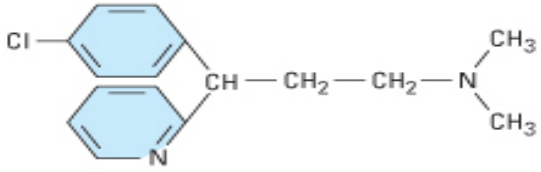
Tripelennamine

PIPERAZINE DERIVATIVE



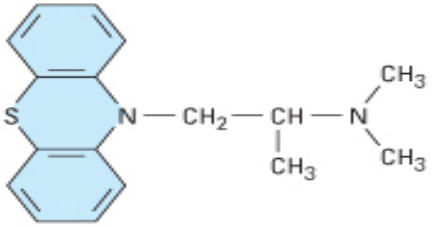
Cyclizine

ALKYLAMINE DERIVATIVE



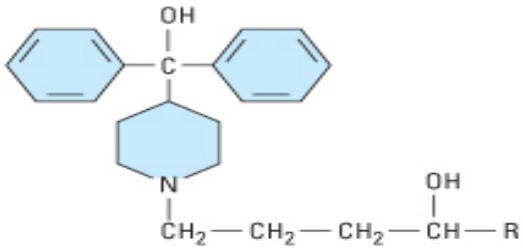
Chlorpheniramine

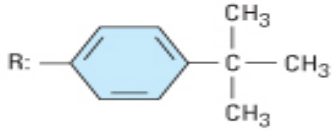
PHENOTHIAZINE DERIVATIVE



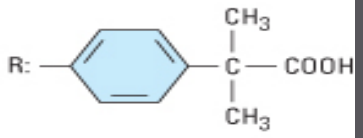
Promethazine

PIPERIDINE DERIVATIVES





Terfenadine



Fexofenadine

First-Generation Antihistamines (Short acting)

These have duration of action from 3 to 6 hours except clemastine and Meclizine that are long acting.

1. Ethanolamines

Carbinoxamine

Clemastine

Diphenhydramine

Dimenhydrinate

2. Ethylenediamines

Pyrilamine

Tripelennamine

Mepyramine

3. Alkylamines

Chlorpheniramine

Brompheniramine

4. Piperazines

Cyclizine

Hydroxyzine

Meclizine

Oxatomide

5. Phenothiazines

Promethazine

6. Piperidines

Cyproheptadine

7.Arylalkylamines;

Triprolidine

8.Phenindenes;

Mebhydrolin

9.Miscellaneous;

Ebastine

2. Second-Generation Antihistamines (Long acting)

All have duration of action from 12-24 hours.

1. Piperidines

Loratadine

Desloratadine

Fexofenadine

2. Piperazines

Cetirizine

Levocetirizine

Table 16–2. Some H_1 antihistaminic drugs in clinical use.

Drugs	Usual Adult Dose	Anti-cholinergic Activity	Comments
FIRST-GENERATION ANTIHISTAMINES			
Ethanolamines			
Carbinoxamine (Clistin)	4–8 mg	+++	Slight to moderate sedation
Dimenhydrinate (salt of diphenhydramine) (Dramamine)	50 mg	+++	Marked sedation; anti-motion sickness activity
Diphenhydramine (Benadryl, etc)	25–50 mg	+++	Marked sedation; anti-motion sickness activity
Doxylamine	1.25–25 mg	nd	Marked sedation; now available only in OTC "sleep aids"
Ethylaminediamines			
Pyrilamine (Neo-Antergan)	25–50 mg	+	Moderate sedation; component of OTC "sleep aids"
Tripelennamine (PBZ, etc)	25–50 mg	+	Moderate sedation
Piperazine derivatives			
Hydroxyzine (Atarax, etc)	15–100 mg	nd	Marked sedation
Cyclizine (Marezine)	25–50 mg	–	Slight sedation; anti-motion sickness activity
Meclizine (Bonine, etc)	25–50 mg	–	Slight sedation; anti-motion sickness activity
Alkylamines			
Brompheniramine (Dimetane, etc)	4–8 mg	+	Slight sedation
Chlorpheniramine (Chlor-Trimeton, etc)	4–8 mg	+	Slight sedation; common component of OTC "cold" medication
Phenothiazine derivatives			
Promethazine (Phenergan, etc)	10–25 mg	+++	Marked sedation; antiemetic
Miscellaneous			
Cyproheptadine (Periactin, etc)	4 mg	+	Moderate sedation; also has antiserotonin activity
SECOND-GENERATION ANTIHISTAMINES			
Piperidines			
Fexofenadine (Allegra)	60 mg	–	Lower risk of arrhythmia
Miscellaneous			
Loratadine (Claritin)	10 mg	–	Longer action
Cetirizine (Zyrtec)	5–10 mg	–	

Nd, no data found.

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

Mechanism of Action

At therapeutic doses, the first- and second-generation antihistamines are equilibrium-competitive inhibitors of H1-receptor–mediated responses. The therapeutic effectiveness of these drugs arises from their capacity to block histamine mediated vasoconstriction, microvascular permeability enhancement, and sensory nerve terminal stimulation.

The antimuscarinic activity of several first-generation H1-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 alpha adrenoceptors, whereas cyproheptadine is an antagonist at serotonin receptors. Diphenhydramine , pyrilamine, and promethazine are effective local anesthetics.

Pharmacological effects:

1. Sedation;

A common effect of first-generation H1 antagonists is sedation. Compulsive use has not been reported. At very high toxic dose levels, marked stimulation, agitation, and even convulsions may precede coma. Second-generation H1 antagonists have little or no sedative or stimulant actions.

2. Antinausea and antiemetic actions

The antimuscarinic activity of several first-generation H1-blockers may account for their effectiveness in combating motion sickness.

3. Antiparkinsonism effects;

The antimuscarinic activity of several first-generation H1-blockers may account for their effectiveness to suppress parkinsonian symptoms.

Antimuscarinic action of antihistamines may be responsible for some of the benefits reported for nonallergic rhinorrhea but may also cause urinary retention and blurred vision.

4. Adrenoceptor-blocking actions;

Alpha-receptor-blocking effects can be demonstrated for many H1 antagonists, especially those in the phenothiazine subgroup, eg, promethazine. This action

may cause orthostatic hypotension in susceptible individuals. Beta-receptor blockade is not observed.

5. Serotonin-blocking action;

Strong blocking effects at serotonin receptors have been demonstrated for some first-generation H1 antagonists, notably cyproheptadine.

7. Local anesthesia;

Several first-generation H1 antagonists are potent local anesthetics. They block sodium channels in excitable membranes in the same fashion as procaine and lidocaine. Diphenhydramine and promethazine are

actually more potent than procaine as local anesthetics. They are occasionally used to produce local anesthesia in patients allergic to conventional local anesthetic drugs. A small number of these agents also block potassium channels.

Clinical Uses

1. Allergic reactions

The H1 antihistaminic agents are often the first drugs used to prevent or treat the symptoms of allergic reactions. In allergic rhinitis, urticaria, Allergic conjuctivitis in which histamine is the primary mediator, the H1 antagonists are the drugs of choice and are often quite effective. However, in bronchial asthma, which involves several mediators, the H1 antagonists are largely ineffective. However, the H1-antagonists are not drugs of choice in acute Anaphylactic emergencies or the viral-caused common

cold.

2. Motion sickness and vestibular disturbances

Scopolamine and certain first-generation H1 antagonists are the most effective agents available for the prevention of motion sickness. Diphenhydramine , dimenhydrinate, cyclizine, and meclizine have Anticholinergic activity and are the preferred antihistaminic agents for reducing the symptoms of motion sickness.

3. Nausea and vomiting of pregnancy

Several H1-antagonist drugs have been studied for possible use in treating "morning sickness." The piperazine derivatives and Doxylamine were withdrawn b/c of teratogenic effects.

4. Parkinson's disease

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

5. For induction of sleep:

Many H1-receptor blocking drugs have sedative properties, and some have been used in over-the Counter sleep aids. The most widely used H1-blockingdrugs for sleep induction are diphenhydramine, promethazine, and pyrilamine.

Adverse Effects

Sedation is the most frequent adverse reaction to the first-generation antihistamines. 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 antihistaminesmay develop after prolonged administration. Teratogenic effects of the piperazine antihistamines have been shown in animal studies.

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.

Tolerance:

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