Autacoids and related drugs

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Autacoids and Related Drugs

- Autacoid This term is derived from Greek:

  autos-self , akos-healing substance or remedy.
- These are diverse substances produced by a wide variety of cells in the body, having intense biological activity, but generally act locally (e.g.within inflammatory pockets) at the site of synthesis and release.
- They have also been called 'local hormones'.
- However, they differ from 'hormones' in two important ways-

1. hormones are produced by specific cells, and
2. are transported through circulation to act on distant target tissues.

Autacoids
(short acting endogenous mediators, usually acting as part of an inflammatory response)

- Bradykinin
- Eicosanoids
  - Prostaglandins, thromboxanes, leukotrienes
- Histamine
- Kallidin
- Platelet activating factor (PAF)
- Serotonin (5-hydroxytryptamine, 5-HT)

Autacoids are involved in a number of physiological and pathological processes(especially reaction to injury and immunological insult) and even serve as transmitters or modulators in the nervous system, but their role at many sites is not precisely known. A number of useful drugs act by modifying their action or metabolism.

The classical autacoids are-

Amine autacoids :Histamine, 5-Hydroxytryptamine (Serotonin)

Lipid derived autacoids :Prostaglandins,Leukotrienes, Platelet activating factor

Peptide autacoids :Plasma kinins (Bradykinin, Kallidin), Angiotensin

In addition, cytokines (interleukins, TNFα, GM-CSF etc.) and several peptides like gastrin,somatostatin, vasoactive intestinal peptideand many others may be considered as autacoids.

Histamine and Antihistamines

'Antihistamines' means classical H1 receptor antagonists unless otherwise specified

Drug list items

- cetirizine (Zyrtec®)
- chlorpheniramine (Chlor-Trimeton®)
- diphenhydramine (Benadryl®)
- disodium cromoglycate (cromolyn, Intal®)**
- fexofenadine (Allegra®)
- histamine
- hydroxyzine (Atarax®)
- loratadine (Claritin®)
- promethazine (Phenergan®)
- scopolamine (Transderm Scop®)**
- tripelennamine (PBZ)

Histamine (tissue amine, also 'enteramine'):
another potent biogenic amine
(normally acts locally, an 'autacoid')

- Synthesized by decarboxylation from an amino acid precursor, histidine
- Stored in granules in certain cells (mast cells, basophils, enterocytes)
- Released in response to certain stimuli (Ca dependent exocytosis)
- Eliminated by oxidative deamination and/or transmethylation

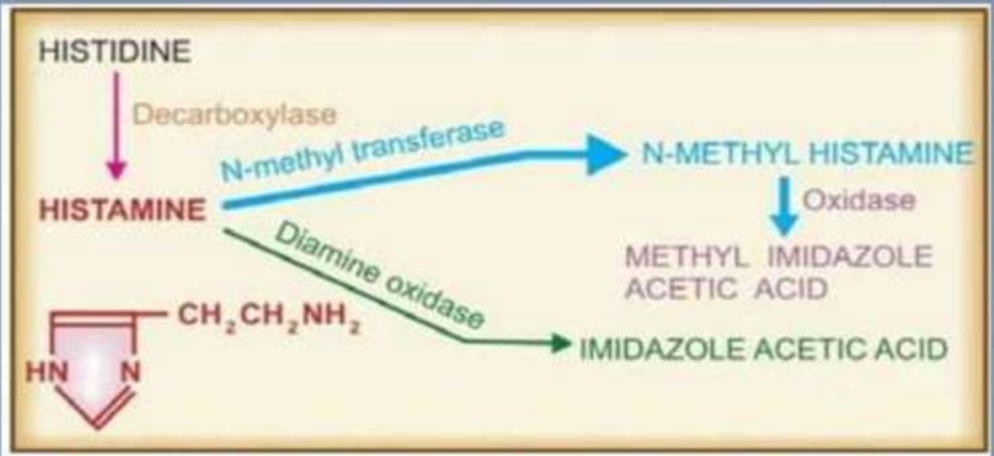


Fig. 11.1: Synthesis and degradation of histamine

Histamine is B imidazolylethylamine. It is synthesized
locally from the amino acid histidine and degraded rapidly by oxidation and methylation (Fig. 11.1). In mast cells, histamine (positively charged) is held by an acidic protein and heparin (negatively charged) within intracellular granules. When the granules are extruded by exocytosis,
Na ions in e.c.f. exchange with histamine to release it free (Fig. 11.2). Increase in intracellular cAMP inhibits histamine release. Histamine is inactive orally because liver degrades all

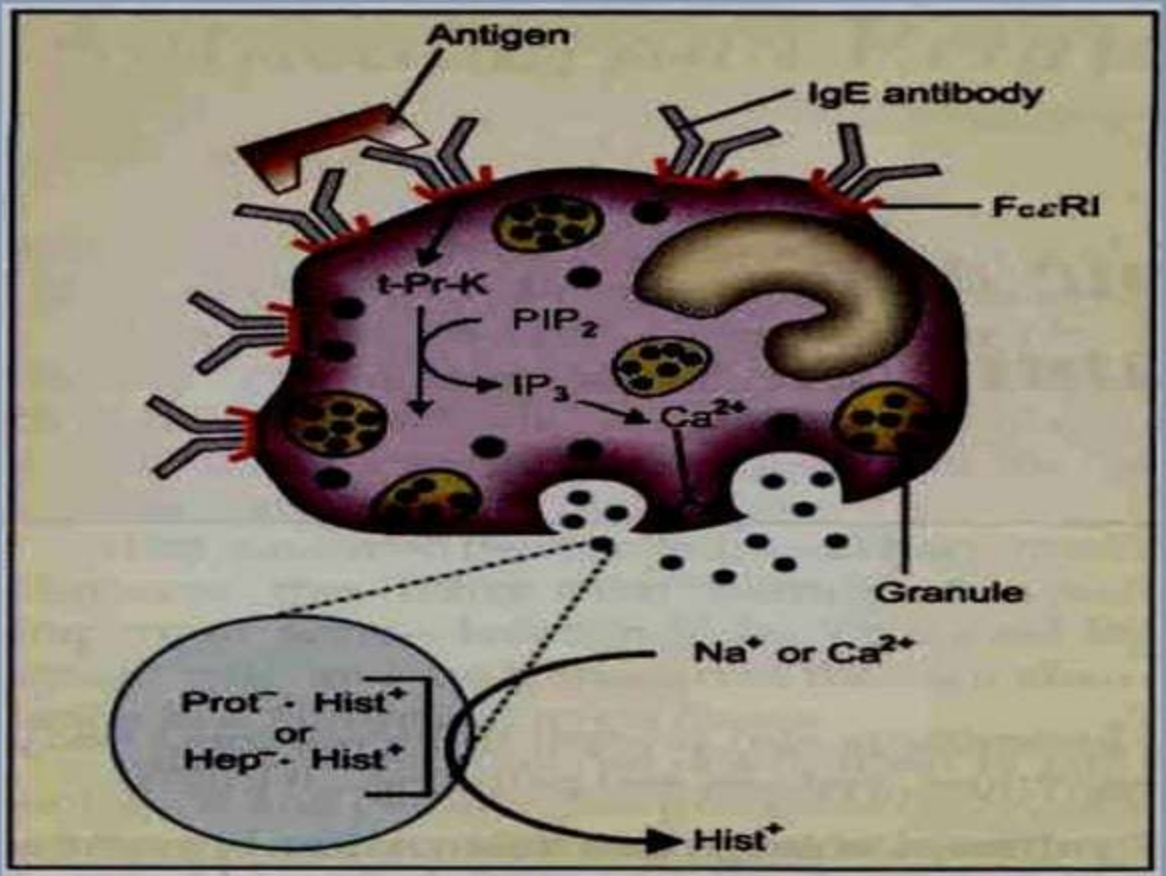


Fig. 11.2: Mechanism of antigen-antibody reaction induced release of histamine from mast cell.

Histamine receptors

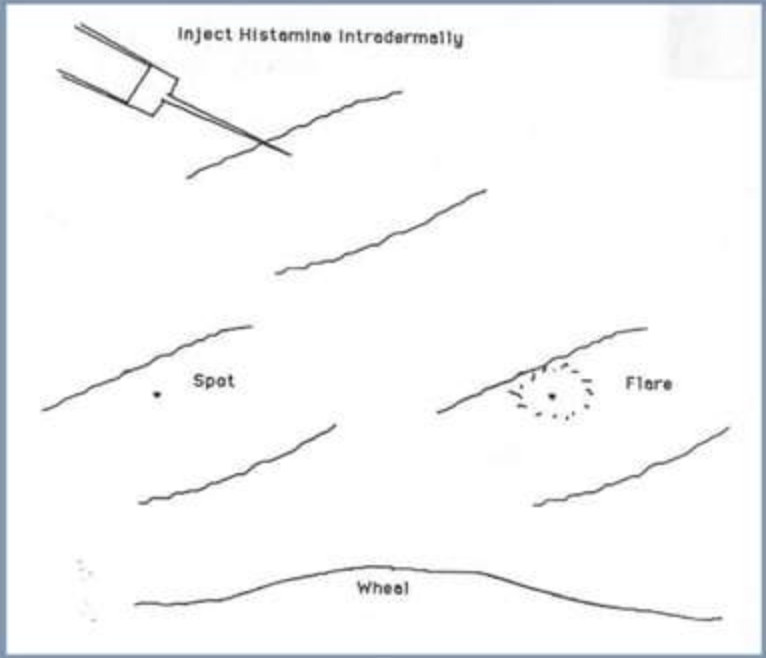
- H1 - smooth muscle, exocrine glands, vascular endothelium, brain; coupled to phospholipase C, leading to IP3 and diacylglycerol (DAG)

- H2 - parietal cells, heart, vascular smooth muscle, mast cells, brain; coupled to cAMP production

- H3 - presynaptic, brain, myenteric plexus (no therapeutic applications, yet)

Histamine in the skin: the Triple Response of Lewis

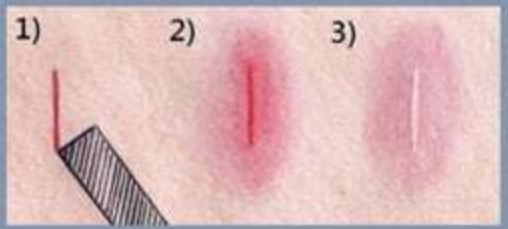
- Red spot
- Flare
- Weal



Inflammation-2

Lewis Triple Response:

- **Flush**: capillary dilatation.
- **Flare**: arteriolar dilatation.
- **Weal**: exudation, edema.



Effects of histamine

- Decreased peripheral vascular resistance (mediated by H1 and H2) (flushing, headache!)
- Increased vascular permeability, especially postcapillaries, local edema (H1)
- Stimulation of nerve endings (pain!)
- Tachycardia, direct (H2) and reflex
- Increased gastric acid secretion (H2) and GI motility (H1)

Histamine release: Promoted by many compounds

- Therapeutic:
  morphine, d-tubocurarine, aminoglycosides
  (remember "Red neck syndrome" ??)

- Experimental:
  compound 48/80 (was tested as antihypertensive)

- Unknown:
  cause of hives is rarely determined

- Antigen-antibody reactions

Anaphylaxis

- Type I allergic response
  (immediate hypersensitivity reaction)
- Mediated by IgE antibodies
- IgE binds to receptors on mast cells and basophils
- Fab portion of antibody binds antigen and causes (moderate to massive) release of:
  - histamine
  - leukotrienes
  - prostaglandins
  - etc.

Common causes of anaphylactic and anaphylactoid reactions

- **IgE-mediated Anaphylaxis**

- Peanuts, seafood, eggs, milk, grains
- Venoms
- Foreign proteins
- Some exercise-induced bronchospasm

- **Non-IgE-mediated Anaphylactoid**

- NMJ blockers, opioids, plasma expanders
- Aminoglycosides
- Protamine
- Radiocontrast media
- Urticaria of cold, heat, sun
- Some exercised-induced bronchospasm

Anaphylaxis: Effects and Treatment

(may involve release of mediators in addition to histamine)

- Decreased blood pressure
- Decreased cardiac output
- Bronchoconstriction and increased pulmonary secretions
- Pruritis

- Treatment: Epinephrine - not initially antihistamines (epinephrine is a physiological antagonist of histamine, not a pharmacological antagonist)

(alpha-1 vasoconstriction, beta-1 increased HR, beta-2 bronchodilation)

Three mechanistically different approaches to minimize histamine reactions

- Physiological antagonism (e.g., epinephrine)
- Inhibit the release of histamine (e.g., cromolyn)
- Pharmacological antagonism (antihistamines)

disodium cromoglycate (cromolyn, Intal®)

- Decreases histamine release from mast cells (and decreases release of SRS-A)
- Administration: inhalation of nebulized solution (formerly powder, irritating)
- May be useful in prophylaxis of histamine release, but does not antagonize the effects of histamine
- Similar mechanism and effects by nedocromil (Tilade®)

Cromolyn (Intal®)

- Indications:
  - Adjunct in treatment of severe perennial asthma
  - Prevention and treatment of allergic rhinitis
  - Prevention of exercise induced bronchospasm
  - Systemic mastocytosis (mast cell 'dumping')
  - Allergic ocular disorders

- Contraindications
  - Acute asthma
  - Bronchospasm

Cromolyn: Adverse reactions

- Cough
- Wheezing
- Headache
- Rash
- Nausea

H1 antihistamines: diverse pharmacological properties

- Antagonize H1 receptors (±)
- Prophylaxis of motion sickness & vomiting
- Inhibition of allergic rhinitis
- Useful symptomatic relief
  pollinosis, conjunctivitis, urticaria (but do not use topically !)

General properties of *first generation* H1 antihistamines

- Lipid soluble - CNS penetration and effects
- Well absorbed
- Metabolized in the liver
- Half life about 5-6 hours
- Adverse reactions
  - SEDATION, DROWSINESS
  - headache, nausea & vomiting
  - cough
  - constipation, diarrhea
  - dry mouth, blurred vision, urinary retention

H1 antihistamines: overdosage

- Fever
- Excitement
- Pupillary dilatation
- Hallucinations
- Convulsions

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REMEMBER

Hot as a stove...

Red as a beet...

Dry as a bone...

Mad as a hatter

Some *second generation* ('non-drowsy') H1 antihistamines

- terfenadine (Seldane®), the pioneer of this second generation (NOW WITHDRAWN)
- astemizole (Hismanal®) (NOW WITHDRAWN)
- fexofenadine (Allegra®)
  (active metabolite of terfenadine)
- cetirizine (Zyrtec®)
- loratadine (Claritin®)

Second generation antihistamines are recommended as the first line in treatment of allergic rhinitis by The American College of Allergy Asthma and Immunology (Ann. Allergy Asthma & Immunology, Nov. 1998). Avoids drowsiness of first generation antihistamines and major adverse reactions of injected corticosteroids.

Terfenadine (Seldane®) blocks K channels: May cause torsades de pointes

- There is normally a large first pass effect resulting in creation of carboxy-terfenadine (fexofenadine) by CYP3A4

- Erythromycin, ketoconazole and other drugs that inhibit CYP3A4 promote accumulation of unchanged terfenadine and, thus, increased the risk of torsade de pointes - prompting withdrawal of terfenadine (similar effects with astemizole, Hismanal®, also withdrawn)

General properties of *second generation* H1 antihistamines

- Lipid soluble structure with a highly ionized functional group - less CNS penetration - more selective for peripheral H1 antagonism (less useful in other indications)
- Well absorbed
- Metabolized in the liver
- Half life about 5-6 hours

- (Huge potential market, direct consumer advertising)

Indications for antihistamine examples

First generation

- **promethazine**
- Rhinitis
- Urticaria & angioedema
- Allergic conjunctivitis
- Anaphylaxis (with EPI)

- Pre/post op sedation
- Prevention of N&V
- Prevention of motion sickness
- Adjunct to pain meds (esp. hydroxyzine)
- (local anesthetic)

Second generation

- **fexofenadine**
- Seasonal allergic rhinitis
- Urticaria, chronic

Table 11.1: Distinctive features of three types of histaminergic receptors

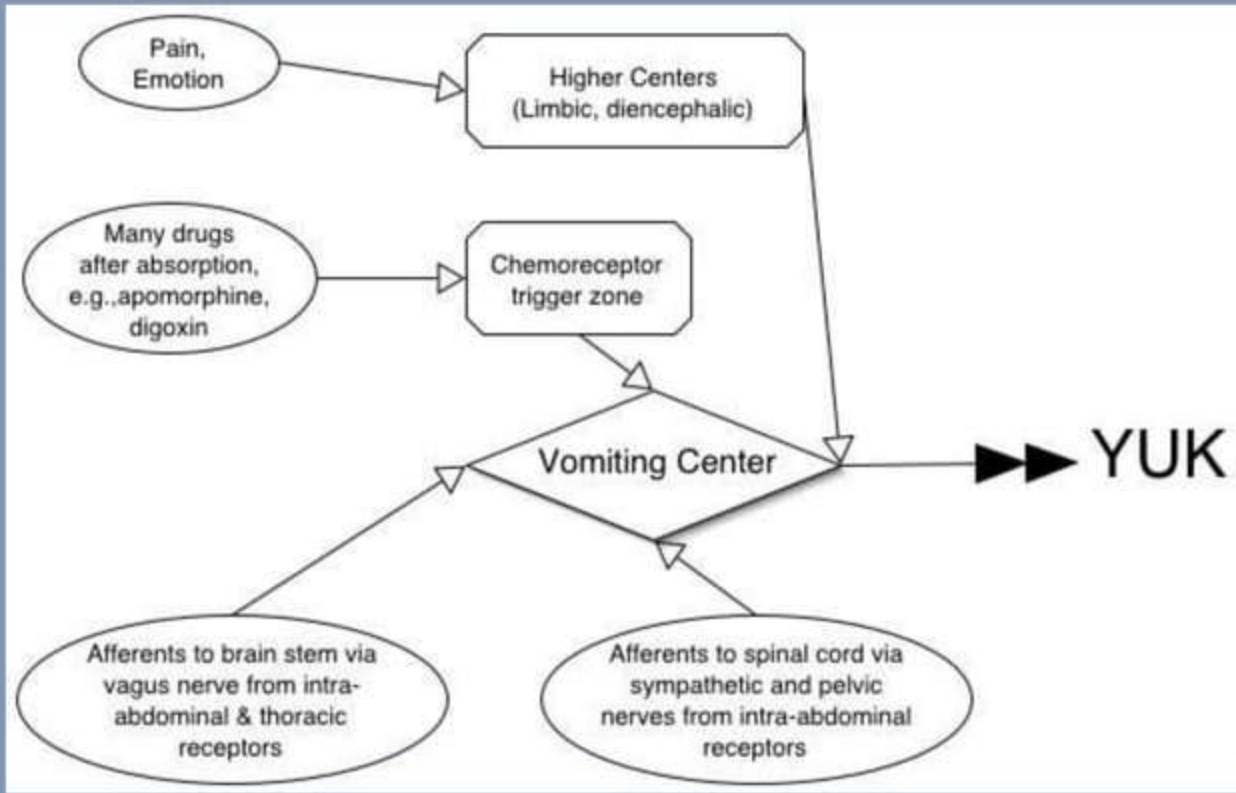
	H_1	H_2	H_3
1. Selective agonists (relative selectivity H_1: H_2)	2-Methyl histamine (8:1) 2-Pyridylethylamine(30:1) 2-Thiazolyl ethylamine (90: 1)	4-Methyl histamine (1:170) Dimaprit (1:2000) Impromidine (1:10,000)	(R) α-Methyl histamine (H_1: H_3 1:3000) Imetit
2. Selective antagonists (relative selectivity H_1: H_2)	Mepyramine (6000:1) Chlorpheniramine (15000:1)	Cimetidine (1: 500) Ranitidine (1 : >500)	Thioperamide (H_1: H_3 1: 23000) Impromidine (H_2 agonist) Clobenpropit
3. Receptor type	G-protein coupled	G-protein coupled	G-protein coupled
4. Effector pathway	PIP_2 hydrolysis → IP_3/DAG : Release of Ca^{2+} from intracellular stores; Protein kinase-C activation	Adenylyl cyclase activation — cAMP ↑ — phosphorylation of specific proteins	a) Restricting Ca^{2+} influx b) K^+ channel activation c) cAMP ↓
5. Distribution in body: actions mediated	a) Smooth muscle (intestine, airway, uterus) — contraction b) Blood vessels i) Endothelium: Release of NO and, PGI_2 — vasodilatation. widening of gap junctions — increased capillary permeability ii) Smooth muscle — vasoconstriction. c) Afferent nerve endings — stimulation d) Ganglionic cell — stimulation. e) Adrenal medulla — release of CAs. f) Brain — transmitter.	a) Gastric glands — acid secretion b) Blood vessels (smooth muscle) — dilatation c) Heart Atria: +ive chronotropy Ventricles: +ive inotropy d) Uterus (rat) — relaxation e) Brain — transmitter	a) Brain (presynaptically) — inhibition of histamine release — sedation b) Lung, spleen, skin, gastric mucosa — decrease histamine release c) Ileum — inhibition of ACh release from myenteric plexus neurones d) Certain blood vessels — inhibit NA release — vasodilatation

PIP_2 — Phosphatidyl inositol bisphosphate; IP_3 — Inositol trisphosphate; DAG — Diacylglycerols;

EDRF — Endothelium dependent relaxing factor; PGI_2 — Prostacyclin;

CAs — Catecholamines; cAMP — Cyclic 3', 5' adenosine monophosphate; ACh — acetylcholine

Input and integration of the vomiting reflex



Worth noting.....

- First generation antihistamines are virtually without value in the treatment of asthma; may be relatively contraindicated. The main benefit in pruritis may be sedation.....on the other hand, a main cause of driver drowsiness may be traced to antihistamines.....

- Second generations antihistamines may be useful (off label)
  in some patients with asthma (e.g., 20 mg of cetirizine has a bronchodilator action additive to that of albuterol in subjects with FEV1 of 50-80% of predicted, Spector et al., 1995).