AUTACOIDS

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INTRODUCTION

- AUTACOIDS auto=self akos=healing/remedy
- Local Hormones

"An organic substance, such as a hormone, produced in one part of organism and transported by the blood or lymph to another part of the organism where it exerts a physiologic effect on that part".

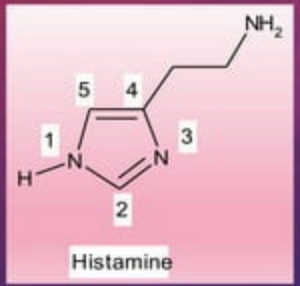
CLASSIFICATION

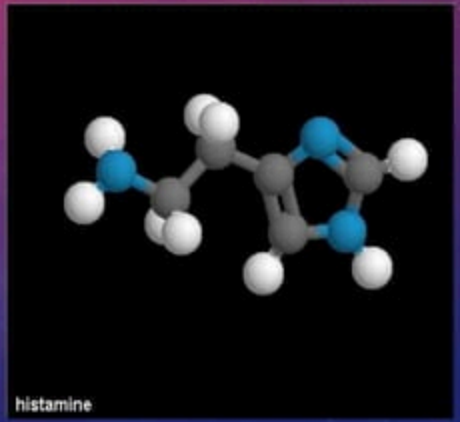
- **Amine derived**: Histamine (amino acid: Histidine), Serotonin (Tryptophan)
- **Peptide derived**: Angiotensin, Bradykinin
- **Lipid derived**: Prostaglandins, Leukotrienes, Interleukins, Platelet Activating Factor

AMINE AUTACOIDS

- DERIVED FROM NATURAL AMINO ACIDS
- HISTAMINE AND SEROTONIN are the major autacoids in this class

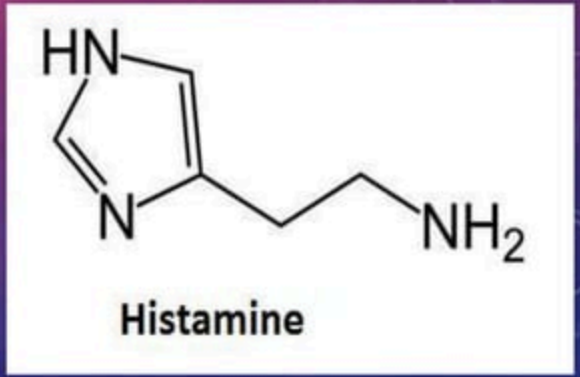
HISTAMINE





INTRODUCTION

- Imidazole ethylamine
- Formed from the amino acid *Histidine*
- Important inflammatory mediator
- Potent biogenic amine and plays an important role in inflammation, anaphylaxis, allergies, gastric acid secretion and drug reaction
- As part of an immune response to foreign pathogens, produced by Basophils and mast cells found in nearby connective tissues.



Histamine

SITES OF HISTAMINE RELEASE

1) Mast cell site:

- Pulmonary tissue (mucosa of bronchial tree)
- Skin
- GIT(intestinal mucosa)

Conc. Of histamine is particularly high in these tissues

2) Non-mast cell sites:

- CNS (neurons)
- Epidermis of skin
- GIT(gastric cells)
- Cells in regenerating or rapidly growing tissues
- Basophils (in the blood)

SYNTHESIS

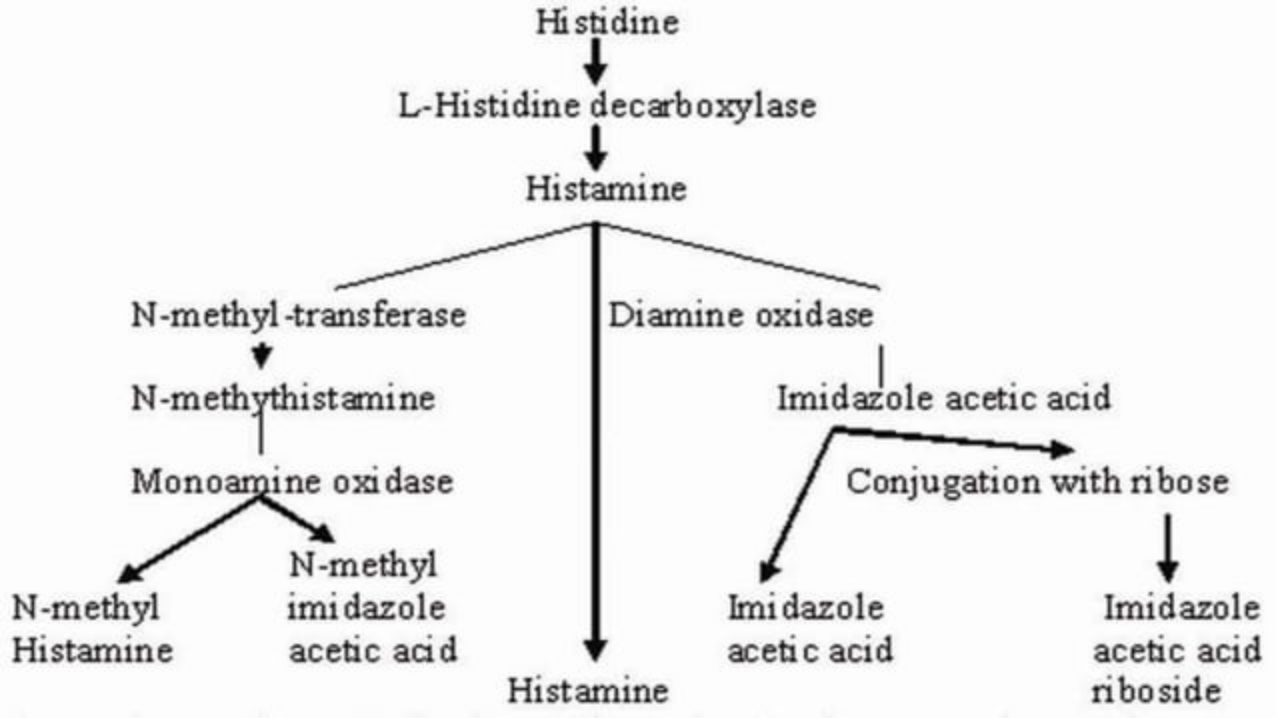
- Decarboxylation of amino acid L-histidine catalyzed by L-histidine decarboxylase.

- Storage sites:
  - perivascular tissue – mast cell
  - circulation – basophil (bound to chondroitin SO4)
  - others – GIT, lungs, skin, heart, liver, neural tissue, reproductive mucosa, rapidly growing tissues and body fluids

METABOLISM

Major pathways

- Deamination – small intestine, liver, kidney and monocytes
- Methylation – small intestine, liver, skin, kidney, thymus & leukocytes


Histidine
L-Histidine decarboxylase
Histamine
N-methyl-transferase
Diamine oxidase
N-methythistamine
Imidazole acetic acid
Monoamine oxidase
Conjugation with ribose
N-methyl Histamine
N-methyl imidazole acetic acid
Histamine
Imidazole acetic acid
Imidazole acetic acid riboside

MECHANISM OF ACTION

Histamine is an autacoid, which means it acts similarly to a local hormone, near its site of synthesis. It is produced as part of the local immune response to invading bodies and triggers inflammation.

Histamine exerts its effects by binding to histamine receptors on cells' surfaces.

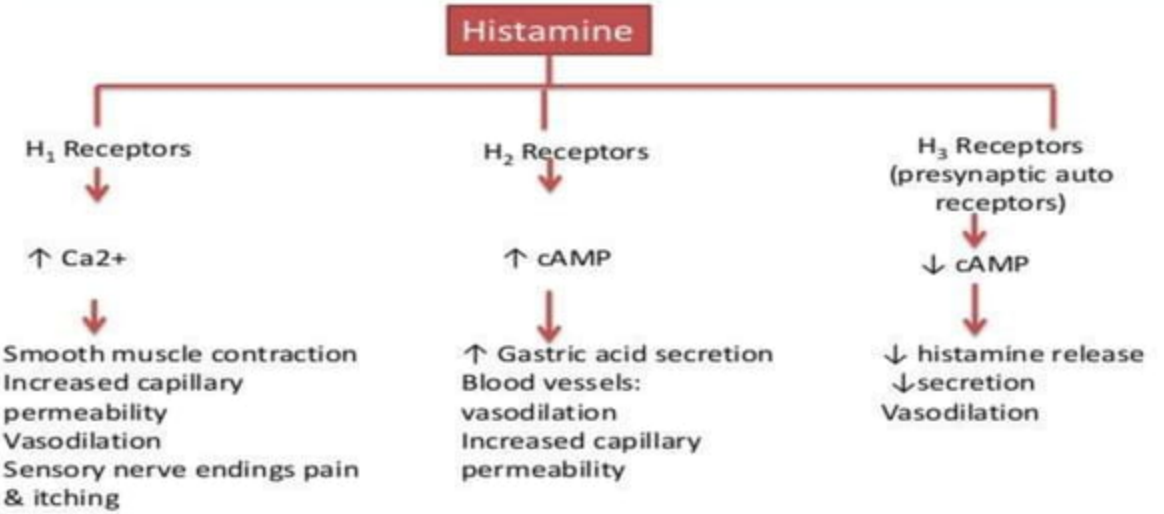
There are four types of histamine receptor: H1, H2, H3 and H4. The binding of histamine to these receptors stimulates them to produce functional responses:

- The H1 histamine receptor plays an important role in allergic response and is widely distributed throughout the peripheral nervous system, particularly the smooth muscle. Activation of the H1 receptor causes blood vessel dilation, increased vessel permeability, stimulation of sensory nerves in the airways and bronchoconstriction. In addition, activation of this receptor promotes the chemotaxis of eosinophils, which can lead to nasal congestion, sneezing and rhinorrhea.

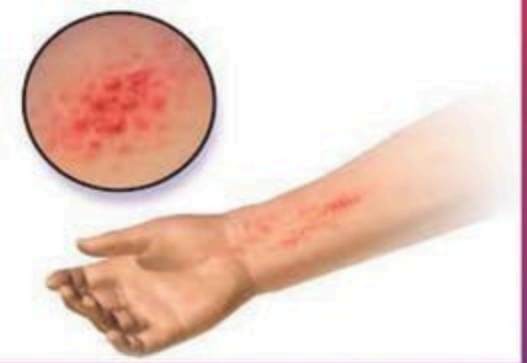
- The H2 receptor is found on the parietal cells within the stomach, heart and to a limited extent, in immune cells and vascular smooth muscle. Activation of the H2 receptor stimulates vasodilation and release of the gastric acids required for digestion.

- The H3 histamine receptor is a presynaptic autoreceptor found on nerve cells that contain histamine. It is widely distributed throughout the central nervous system, with the greatest expression found in the cortex, caudate nucleus, thalamus, hypothalamus, olfactory tubercle and hippocampus. The diverse distribution of the H3 receptor throughout the cortex suggests this receptor is able to modulate many neurotransmitters such as dopamine, GABA, acetylcholine and norepinephrine in the central and peripheral nervous systems.

Mechanism of Action of Histamine

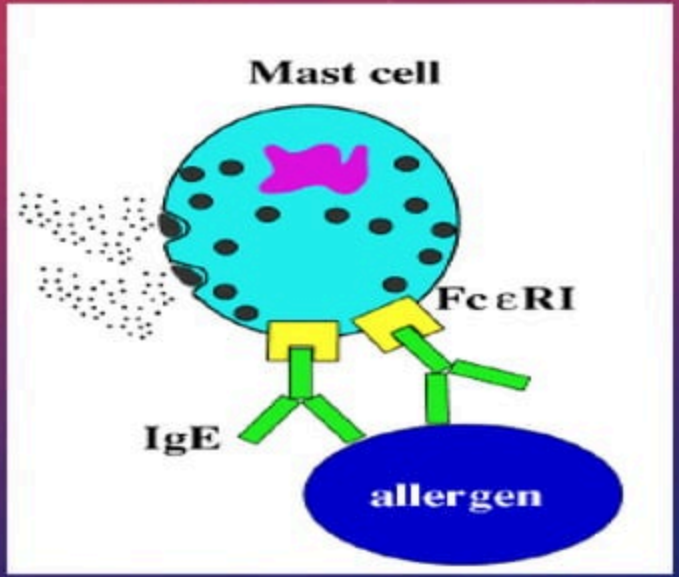


- The H4 histamine receptor is mainly found on immune cells and tissues including peripheral blood leukocytes, the spleen, bone marrow and thymus. It is also found in the colon, lung, liver and epicanthus. Stimulation of this receptor also mediates the chemotaxis of eosinophils and upregulates adehsion of molecules.



ROLE IN ALLERGY:

- Allergies are caused by a hypersensitivity reaction of the antibody class IgE (which are located on mast cells in the tissues and basophils in the blood)
- When an allergen is encountered, it binds to IgE, which excessively activates the mast cells or basophils, leading them to release massive amounts of histamines


Mast cell
FcεRI
IgE
allergen

- These histamines lead to inflammatory responses ranging from runny nose to anaphylactic shock
- If both parents have allergies, you have a 70% chance of having them, if only one parent does, you have a 48% chance, statistics suggested by American Academy of Asthma, Allergies and Immunology.

HISTAMINE ANTAGONISTS

Anithistamines are drugs used to block the activity of histamines, by preventing the ability of histamine to bind to histamine receptors. These agents are therefore referred to as histamine antagonists.

HISTAMINE ANTAGONISTS

H1 receptor antagonist

1) Sedative (first generation) antihistamines: Highly lipid soluble and easily enters into the CNS:

a) Potent and marked sedative:

• Promethazine (phenergan) *widely used* • Diphenhydramine Dimenhydrinate

b) Potent and moderate sedative:

• Chloryclizine • Chlorpheniramine • Tetrahydeoxy carboline

c) Less potent and less sedative: • Mepyramine • Pheniramine(avil)

2) Non-sedative (second generation) antihistamines: Less lipid soluble therefore cannot enter into the CNS:

• Cetrizine • Terfenadine • Astemizole • Ketotifen • Cyclizine

H1 RECEPTOR ANTAGONISTS

Pharmacokinetics:

- Well absorbed from GIT (oral)
- Onset – 30 minutes, duration – 3 to 6 hours
- Biotransformed in the liver
- Excretion – kidneys

THERAPEUTIC USES:

1. Dermatosis
2. Allergic rhinitis
3. Motion sickness & emesis (cyclizine, meclizine)
4. Parkinson's disease (Diphenhydramine)
5. Sedative Agent (Promethazine)
6. Preanesthetic Medication

ADVERSE EFFECTS

1. CNS : sedation, agitation, nervousness, delirium, tremors, incoordination, hallucinations, & convulsions - common in first generation antihistamines
2. GIT : vomiting, diarrhea, anorexia, nausea, epigastric distress, constipation
   - dryness of mouth, throat & airway, urinary retention - first generation
3. Headache, faintness
4. Chest tightness, palpitations, hypotension
5. Visual disturbances

H2 RECEPTOR ANTAGONISTS

H2 blockers are a group of medicines that reduce the amount of acid produced by the cells in the lining of the stomach. They are commonly called **H2 blockers**. They include cimetidine, famotidine, nizatidine and ranitidine.

INDICATIONS

H_2-antagonists are used by clinicians in the treatment of acid-related gastrointestinal conditions, including:

- Peptic ulcer disease (PUD)
- Gastroesophageal reflux disease (GERD/GORD)
- Dyspepsia
- Prevention of stress ulcer (ranitidine)

DRUG INTERACTIONS:

- Cimetidine inhibits cyto p-450 – accumulation of warfarin, phenytoin, theophylline, propanolol, diazepam & phenobarbital
- Ranitidine – weak inhibitor
- Nizatidine & famotidine – do not inhibit cyto P – 450

H_3 RECEPTOR ANTAGONIST

- An **H_3 receptor antagonist** is a classification of drugs used to block the action of histamine at the H_3 receptor.
- Unlike the H_1 and H_2 receptors which have primarily peripheral actions, H_3 receptors are primarily found in the brain and are inhibitory autoreceptors located on histaminergic nerve terminals, which modulate the release of histamine. Histamine release in the brain triggers secondary release of excitatory neurotransmitters such as glutamate and acetylcholine via stimulation of H_1 receptors in the cerebral cortex.

- Consequently, unlike the H_1 antagonist which are sedating, H_3antagonists have stimulant effects, and are being researched as potential drugs for the treatment of neurodegenerative conditions such as Alzheimer's disease.
- Examples of selective H_3 antagonists include clobenpropit, ABT-239, ciproxifan, conessine, A-349,821, and pitolisant.

The ability of the H3 receptor to modulate various neurotransmitters makes this receptor a novel therapeutic target in the relief of symptoms caused by several conditions including movement disorders, obesity, schizophrenia, abnormal sleep/wake patterns and ADHD.

H_4 ANTAGONIST

- The **histamine H4** receptor (H4R) is the newest member of the histamine receptor family. H_4 is highly expressed in bone marrow and white blood cells and regulates neutrophil release from bone marrow and subsequent infiltration in the zymosan-induced pleurisy mouse model. It is also expressed in the colon, liver, lung, small intestine, spleen, testes, thymus, tonsils, and trachea. By inhibiting the H_4 receptor, asthma and allergy may be treated.

The highly selective histamine H_4 antagonist VUF-6002 is orally active and inhibits the activity of both mast cells and eosinophils *in vivo*, and has antiinflammatory and antihyperalgesic effects.

Antagonists

- Thioperamide
- JNJ 7777120
- VUF-6002
- A987306
- A943931

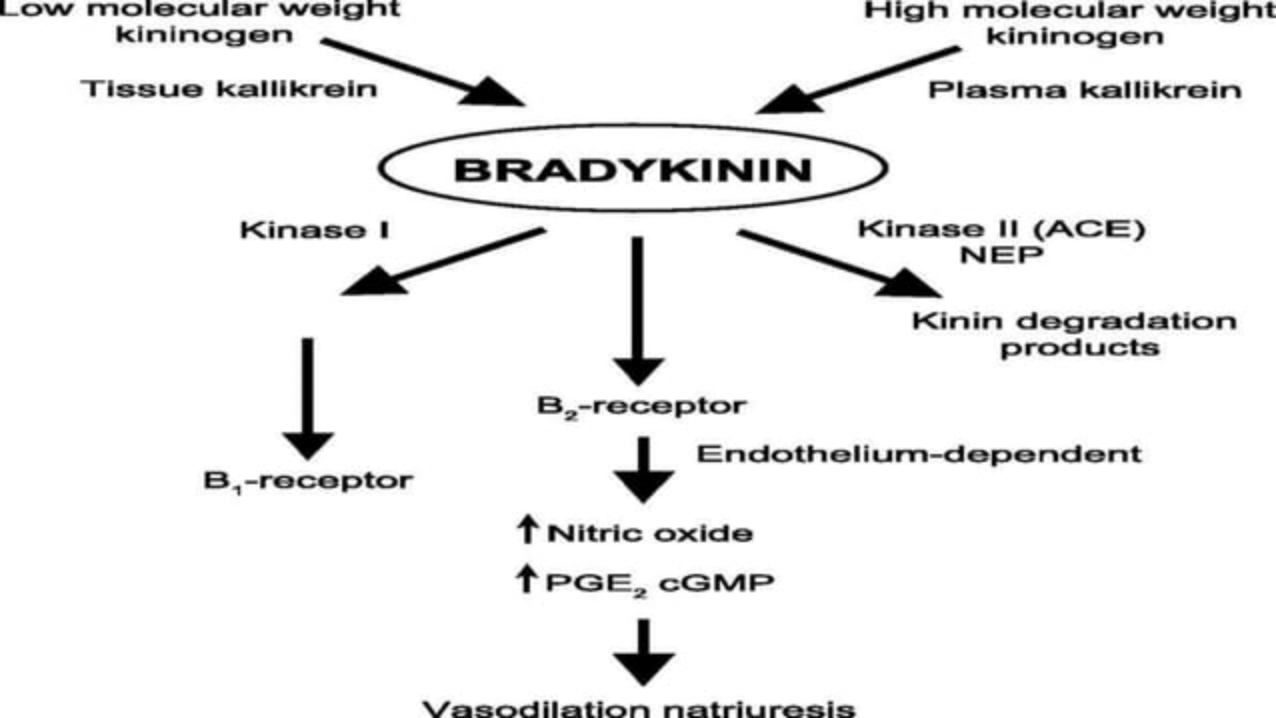
The recent discovery of a fourth histamine receptor (H4), and the realization that it is exclusively expressed on hematopoietic cell types that are most implicated in the development and symptomatology of allergy and asthma, suggests that pharmacological targeting of the H4 receptor, either alone or in combination with H1 receptor antagonists, may prove useful for treating both allergy and asthma.

PEPTIDE DERIVED AUTACOIDS

- THESE ARE DERIVED FROM PROTEINS
- MADE UP OF LONG CHAINS OF POLYPEPTIDES
- MOST IMPORTANT IN THIS CLASS: ANGIOTENSIN, BRADYKININ

BRADYKININ

The kinin-kallikrein system makes bradykinin by proteolytic cleavage of its kininogen precursor, high-molecular-weight kininogen (HMWK or HK), by the enzyme kallikrein. Moreover, there is compelling evidence that plasmin, a fibrinolytic enzyme, is able to generate bradykinin after HMWK cleavage.


Low molecular weight kininogen
High molecular weight kininogen
Tissue kallikrein
Plasma kallikrein
BRADYKININ
Kinase I
Kinase II (ACE) NEP
Kinin degradation products
B2-receptor
B1-receptor
Endothelium-dependent
↑ Nitric oxide
↑ PGE2 cGMP
Vasodilation natriuresis

METABOLISM

In humans, bradykinin is broken down by three kininases:

Angiotensin-converting enzyme (ACE), Aminopeptidase P (APP), and Carboxypeptidase N (CPN), which cleave the 7-8, 1-2, and 8-9 positions, respectively.

BRADYKININ RECEPTORS

- The B_1 receptor (also called bradykinin receptor B1) is expressed only as a result of tissue injury, and is presumed to play a role in chronic pain. This receptor has been also described to play a role in inflammation. Most recently, it has been shown that the kinin B_1 receptor recruits neutrophil via the chemokine CXCL5 production. Moreover, endothelial cells have been described as a potential source for this B_1 receptor-CXCL5 pathway.

- The B_2 receptor is constitutively expressed and participates in bradykinin's vasodilatory role.
- The kinin B_1 and B_2 receptors belong to G protein coupled receptor (GPCR) family.

PHARMACOLOGICAL ACTIONS

Bradykinin is a potent endothelium-dependent vasodilator, leading to a drop in blood pressure. It also causes contraction of non-vascular smooth muscle in the bronchus and gut, increases vascular permeability and is also involved in the mechanism of pain. Bradykinin also causes natriuresis, contributing to the drop in blood pressure.

Overactivation of bradykinin is thought to play a role in a rare disease called hereditary angioedema, formerly known as hereditary angio-neurotic edema.

BRADYKININ INHIBITORS

- Aprotinin (TRASYLOL), the potent inhibitor of kallikrein, has been employed clinically to reduce blood loss in patients undergoing coronary artery bypass surgery, but unfavorable survival statistics in retrospective and prospective studies have resulted in its discontinuation.

A new class of anti-hypertensive agent was developed to inhibit major kinin-degrading enzymes, ACE, and the added inhibition of bradykinin metabolism was expected to enhance therapeutic effectiveness. In phase III clinical trials, the prototype drug omapatrilat was an effective antihypertensive agent but was associated with a 3-fold higher incidence of angioedema than with an ACE inhibitor alone, causing withdrawal of the drug.

More recently, several non-peptide B1 antagonists with *in vivo* activity have been developed the most promising of these is SSR240612, which is orally active and inhibits inflammation and neuropathic pain in animal studies. None has yet been tested clinically.

BRADYKININ INHIBITORS

- Currently, bradykinin inhibitors are being developed as potential therapies for hereditary angioedema. Icatibant is one such inhibitor. Additional bradykinin inhibitors exist. It has long been known in animal studies that bromelain, a substance obtained from the stems and leaves of the pineapple plant, suppresses trauma-induced swelling caused by the release of bradykinin into the bloodstream and tissues.

- Other substances that act as bradykinin inhibitors include aloe and polyphenols, substances found in red wine and green tea.
- Bradykinin is also released by carcinoid tumors, and results in asthma-like symptoms.

Thankyou