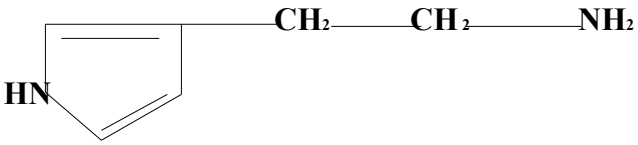
AUTACOIDS

Classification

1. **Decarboxylated amino acid**
    a)Histamine
    b) Serotonin/ 5-HT
2. **Polypeptides:**
    a) Angiotensins
    b) Kinin-kallidin & Bradykinin
    c) Vasoactive intestinal polypeptide
    d) Substance P
3. **Lipids:**
    a) Eicosanoids (Prostaglandins, Leukotrienes, Thromboxane)
    b) Platelet activating factor

Histamine



Histamine is a tissue amines derived from Greek word 'histos' meaning tissue. It is chemically β -aminoethylimidazole synthesized from amino acid histidine by L-histidine decarboxylase. Histamine is rich in plants and animals. It is stored in animal tissues complexed with heparin in mast cells. Principal storage sites are skin, lungs, gastric and intestinal mucosa, liver and placenta. It is also present in some non-mast cells of brain (Hypothalamus), epidermis, gastric mucosa and growing tissues where it is synthesized but not not stored.

Histamine is metabolized by methylation (histamine N-methyl transferase) and oxidation (MAO) to form N-methyl imidazole acetic acid.

Histamine receptors

Three types of histamine receptors have been identified. They are

1. H_1 receptors responsible for bronchial smooth muscle contraction, vascular smooth muscle relaxation and increased capillary permeability and pruritus.
2. H_2 receptors responsible for positive chronotropic and inotropic effect on heart, vasodilation, increased acid secretion, uterine relaxation and neurotransmitter action in the brain.
3. H_3 receptors are presynaptic in the brain. Also present in the lungs, spleen and skin. Stimulation of these receptors causes inhibition of histamine release. Stimulation of H_3 receptors in the bronchi and ileum inhibits Ach release.

Mechanisms:

***H_1* receptors** are coupled to G-protein and act by stimulating phospholipase C (PLC) which breaks membrane phospholipids releasing inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG).

IP_3 releases intracellular Ca^{2+} from endoplasmic reticulum and the increased Ca activates Ca^{2+}-dependent protein kinase C and Phospholipase A_2 .

DAG stimulates protein kinase C which ultimately phosphorylates PKC dependent proteins.

***H_2* receptors** also coupled to membrane bound G- protein which stimulates adenylyl cyclase (AC). AC will increase cyclic AMP concentration which will stimulate cAMP dependent protein kinases. cAMP-dependent protein kinases phosphorylates a series of enzymes.

***H_3* receptors** act by inhibiting AC, or activating K^+ channels or restricting Ca^{2+} channels

Receptor Agonists & Antagonists

	Agonist	Antagonist
H_1 receptor	2-methyl histamine 2-thiazolethylamine	Chlorpheniramine Promethazine Mepyramine Terfenadine
H_2 receptor	4-methylhistamine Betazole Impromidine	Cimetidine Ranitidine Famotidine Nizatidine
H_3 receptor	α- methyl histamine Imetit	Thioperamide Impromidine Buriramide Clobenpropit

Histamine release

Chemical, physical or immunological stimuli cause release of histamine from mast cell.

a) Primary mechanism for histamine release is immunologic during anaphylaxis or allergic reactions. Histamine is released as a result of interaction of Ag with IGE on the surface of mast cell without cell membrane disruption.

b) Some basic drugs (eg. Tubocurarine, morphine, atropine, stilbamidine, polymixin B), stings & venoms, enzymes (proteolytic enzymes), polymers (dextran) etc liberate histamine without an immunological reaction by disrupting the mast cell membrane.

c) Tissue damage (trauma or burns).

d) Agents which increase cAMP formation (eg. B – adrenergic agonist causes histamine release.

Pharmacological effects:

Blood vessel:
Histamine dilates the finer blood vessels (dog, cat) resulting in lowered total peripheral resistance and a fall in systemic blood pressure. Vasodilatation is due to activation of both H_1 (endothelial release of NO) and H_2 (Vascular smooth muscle – cGMP mediated relaxation)

Tripple response:
A triad of phenomena that occur in sequence after the intradermal injection of histamine. First, a red spot develops, spreading outward for a few millimeters, reaching its maximal size within 1 minute and then turning bluish. Next, a brighter red flush of color spreads slowly in an irregular flare around the original red spot. Finally, a wheal filled with fluid forms over the original spot. Also called **triple response of Lewis**.

Histamine headache:
Cluster headache: a migraine-like disorder marked by attacks of unilateral intense pain over the eye and forehead, with flushing and watering of the eyes and nose; attacks last about an hour and occur in clusters.

Heart
Histamine produces positive inotropic and chronotropic effect on heart

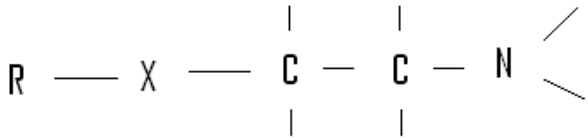
Extravascular smooth muscle:
Histamine contracts the smooth muscle of bronchi, bronchiole, ileum and uterus through H_1 receptors whereas in sheep histamine relaxes bronchioles through H_2 receptors.

Histamine Antagonists

a) Physiological antagonists – Sympathomimetic amines, adrenaline, noradrenaline, ephedrine and others.

b) Destructive antagonist – histamine

c) Pharmacological antagonists – They are the competitive antagonists at H_1 receptors. They are weak bases with the following structure



R is composed of two or more cyclic groups, which may be aromatic, hetero-cyclic or both.
X may be 'nitrogen' as in triplennamine or mepyramine or 'Oxygen' as in diphenhydramine and dimenhydrinate or 'Carbon' as in chlorphenamine.

Compounds containing 'N' at X are usually more powerful than those containing oxygen. Those containing 'Carbon' possess fewer side effects and low toxicity.

d) Inhibitor of histamine release

Sodium cromoglycate is used for prevention of asthma in man. It prevents the release of histamine and SRSA during pulmonary allergic reactions.

Actions:

Antihistaminics are satisfactorily absorbed from the GIT of simple stomached animals, but not in ruminants.

Intravenous injection produces immediate effects but carries the danger of myocardial depression. Antihistaminics counteract the histamine – induced concentration of smooth muscle in the bronchi, intestine and ileum.

Side effects:

1. CNS depression
2. Local anaesthetic effect – but irritant
3. Gastro-intestinal disturbances.
4. Prolonged period of excitement due to intravenous administration
5. Increases the interference with allergic diagnostic procedures, e.g. Tuberculin test.
6. Interference to some extent with the actions of transmitter substances, e.g. Acetylcholine, epinephrine and 5-HT.

Uses of Antihistaminics:

1. Symptomatic treatment of acute and severe allergies, but is is advisable to use adrenaline first followed by oral or intramuscular dosing with an antihistamine. To reduce irritation in small animal oral dosing is done at meal times shortly after feeding.
2. Laminities, purpura, lymphangitis, blue nose and pulmonary emphysema in horse ('heaves' or broken wind'.
3. Acute septic and gangrenous mastitis, retained placenta, myoglobinurea and azoturia.

Toxicity:

Over dosage of antihistamine can cause hyperexcitability and cometimes convulsions. Treatment is symptomatic and usually consists of injection of sedative doses of short acting barbiturates.