

Autocoids

Auto + Cooids

- Auto means 'self', cooids means 'healing or therapy or remedy'.
 - Also known as local hormone
 - Response are localized to affected site
 - Have short half life, hence short duration of action.
 - Doesn't have any similarity with general hormones.
 - Autocoids are released from secreting cells (eg. mast cells) & their effect is localized to specific tissues.
 - General hormones - secreted from one cell and travel along with blood circulation to give their effects in distant tissues/organs.
- Characteristics of Autocoids
- Autocoids involve in physiological or pathological process.
 - Released during allergy/hypersensitivity, inflammation, injury.

Classification of Autocoid

- Amine autocoids - Histamine, 5-Hydroxytryptamine (serotonin)
- Lipid derived - Prostaglandins, leukotrienes, Platelet activating factor.
- Peptide autocoids - Plasma Kinin (Bradykinin, kallidin), Angiotensin.

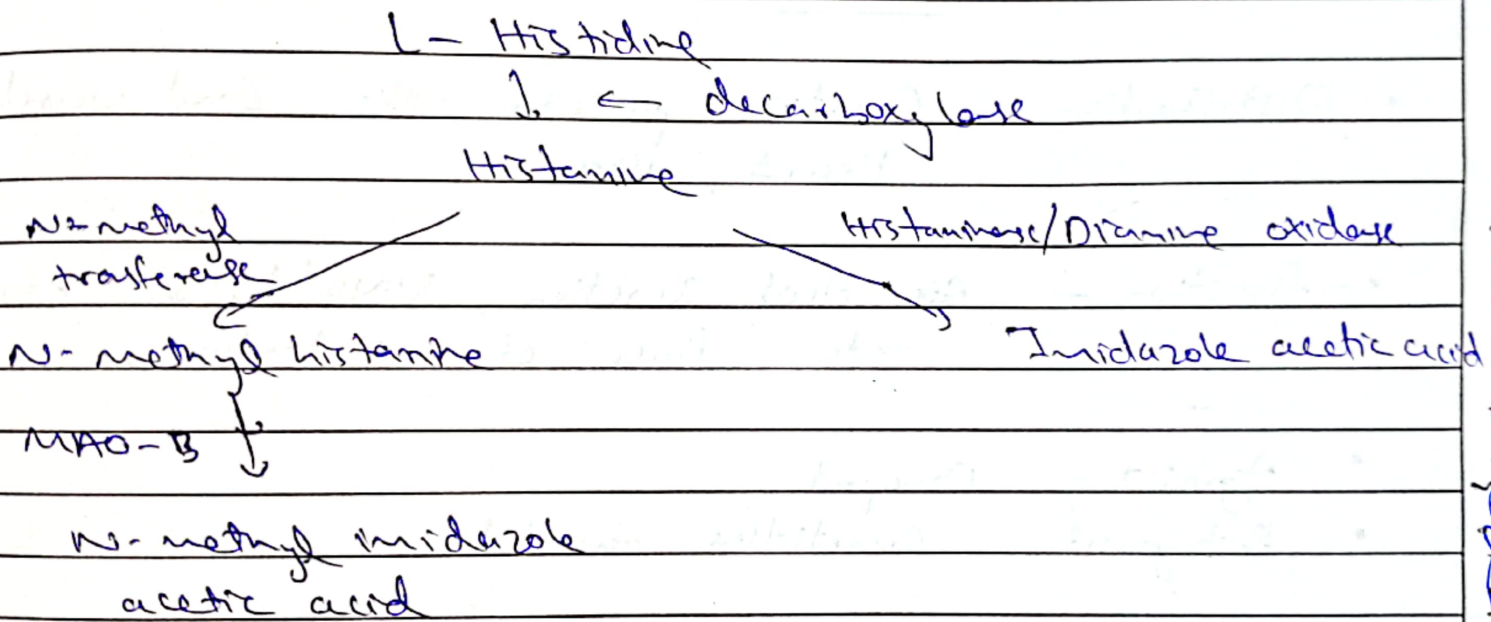
Introduction of Histamine

- first autocoid was discovered & synthesized in 1907.
- natural component of mammalian tissue
- chemical messenger which mediates many cellular processes
- Local action of histamine involves redness, urticaria (skin rash), edema, inflammation,

reactions.

→ Synthesis, storage & destruction

- Histamine is β -imidazole ethylamine derivative
- Biologically active, secreted from the mast cells (lungs, skin, liver) & non-mast cells (brain, GI mucosa).
- It is synthesized locally from the amino acid histidine (in presence of decarboxylase & degraded rapidly by oxidation & methylation)



- Mast cells are predominant site of storage.
- Held by intracellular granules complexed with acidic protein & heparin.
- Increased intracellular cAMP (β -agonist) inhibit the release of histamine.

Histaminergic Receptor

H₁-R

- Distribution - smooth muscle, Blood vessels, CNS, sensory nerves.
- function - contraction of smooth muscle, vasodilation
Increase capillary permeability
- Agonist - Histaprodifen
- Antagonist - Chlorpheniramine, cetirizine

H₂-R

- Distribution - Gastric parietal cells, Blood vessels, Heart, Brain
- function - ~~Acid~~ Acid secretion, vasodilation, heart rate, force of contraction.
- Agonist - Dinaprit
- Antagonist - Cimetidine, famotidine

H₃-R

- Distribution - Brain - presynaptic, lung, spleen, blood vessels.
- function - Decrease histamine, Nor epinephrine, vasodilation

- Agonist - Imetit, α -methyl histamine
- Antagonist - Thioperamide, Pitolisant

H₁-R

- Distribution - Neutrophils, CD4 T-cells
- Function - Production of blood cell types
- Agonist - Imetit
- Antagonist - Thioperamide

- Classification of Antihistamines

- 1- First Generation Antihistamines
 - Highly sedative - Dimenhydrinate, diphenhydramine, promethazine
 - Moderately sedative - Cyproheptadine, pheniramine, Clemastine
 - Mild sedative - Cinnarizine, chlorpheniramine
- 2- Second Generation
 - fexofenadine, loratadine, cetirizine, Levocetirizine, Azelastine, Mizolastine

Pharmacological Actions

1- Antagonism of histamine

- Block histamine induced bronchoconstriction, contraction of intestinal & other smooth muscle & triple response.
- Abolish release of Adr from adrenal medulla.

2- Anti-allergic Action

- Suppress immediate type-I hypersensitivity reaction.
- Treat urticaria, itching and angioedema.

3- CNS Action

- Penetrate blood brain barrier, antagonize H_1 receptor activity in brain.
- 2nd generation are non sedating.
- Helpful in treatment of motion sickness.
- Promethazine is also helpful in reduction of tremor, rigidity in P.D.

4- Anti cholinergic action

- H_1 blockers also antagonize the muscarinic activity.

5- Effect on blood pressure

- On I.V. Inj, most antihistamines cause

fall in BP due to smooth muscle relaxation or alpha blockade effect.

Pharmacokinetics

- Well absorbed orally as well as parenterally.
- Metabolized in liver & excreted through urine.
- Duration of action is 4-6 hrs except Chlorpheniramine, cetirizine, cetrizine, fexofenadine, loratadine, which have duration of action around 12-24 hrs.

Adv -

- sedation
- Diminish alertness & concentration
- Motor incoordination
- fatigue
- Dryness of mouth
- Blurred vision

Serotonin -

- also known as 5-HT or 5-Hydroxytryptamine.
- Discovered in 1948.
- Found in animal as well as plant cell.
- Found 90% in intestinal cells [enterochromaffin cells].
- It is also found in Banana, tomato, pear.
- It regulate mood, sleep & temperature.

* Biosynthesis & Degradation →

Tryptophan

↓ → Hydroxylase

5-Hydroxy tryptophan

↓ → decarboxylase

5-HT

↓ → MOA

5-Hydroxy Indole acetic acid

* 5HT-receptor -

- Classified in 7 types → 5HT₁ - 5HT₇

① 5HT₁ receptor →

- 5HT₁ receptor have 6-subtypes.

5HT_{1A}, 5HT_{1B}, 5HT_{1C}, 5HT_{1D},

5HT_{1E}, 5HT_{1F}

- It act through GPCR pathway.

• distribution →

- CNS, ENS [GIT] & Blood vessel.

function →
• Affect mood, behaviour & vasoconstriction

Agonist - Buspirone
Antagonist - Ergotamine

② SHT₂ receptor →
• It has 3 main subtypes
SHT_{2A}, SHT_{2B}, SHT_{2C}

distribution →
smooth muscle, platelets, cerebral neurons.

function -
• vasoconstriction, smooth muscle contraction
platelet aggregation.

• Agonist - 2-methyl 5HT

• Antagonist - ~~Ondansetron~~ Cyproheptadine

③ SHT₃ receptor -
• distribution - CNS, PNS, ENS

• function - excitation of nociceptive neurons,
anxiety, imesis [vomiting], bradycardia,
hypotension.

• Agonist - 2-methyl 5-HT

• Antagonist - Ondansetron

④ SHT₄₋₇ receptor -

• distribution - CNS & ENS

• function - excitation & ↑ GI motility

• agonist - Cisapride

• antagonist - GR-113808

* Pharmacological action on CNS →

- 5HT act as a neurotransmitter.
- Regulate mood, behaviour, sleep, depression, pain, thermoregulation.
- Regulate sleep cycle by synthesis of melatonin.
- Do not cross blood brain barrier if injective IV.

* Pharmacological action on CVS →

- Contraction of vascular smooth muscle [except skeletal & heart muscle].
- In skeletal & Heart muscle is causes vasodilation & bradycardia.
- 5HT causes platelet aggregation [weak] by $5HT_{2A}$ receptor.

* Pharmacological action on GIT →

- Stimulate peristalsis & gastric secretion.
- Stimulate mucous secretion hence designated as ulcer protective.
- Over production of 5HT leads to tumor of enterochromaffin cells [associated with severe diarrhea]

* Pharmacological action on other organ →

- Stimulate pain perception & itching by $5HT_3$ on afferent nerve.
- Constrict bronchial smooth muscle by less potent than histamine.
- Reduces food intake.