Pharmacology Of Autocoids and Their Antagonists

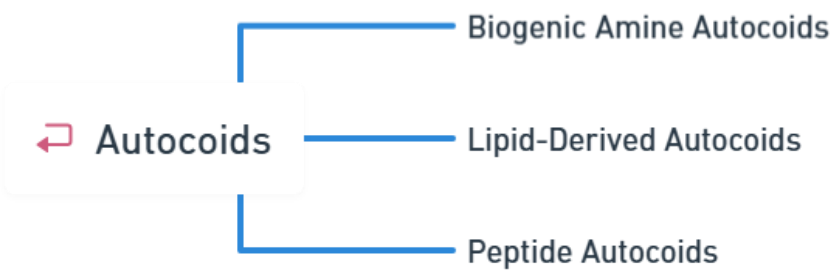
Autocoids and Their Antagonists

Introduction

- Autocoids are locally acting, biologically active substances that are synthesized and released in response to various stimuli and act near their site of synthesis.
- The term "autocoid" is derived from Greek words meaning "self-remedy," highlighting their local action and regulatory roles.
- Autocoids are involved in:
    - Inflammation
    - Pain
    - Allergic reactions
    - Smooth muscle tone modulation
    - Gastrointestinal function
    - Platelet aggregation
    - Neurotransmission
- They exert effects by acting on specific G-protein coupled receptors (GPCRs) or other receptor types on target cells.
- Their actions are short-lived and locally confined, unlike hormones which act at distant sites.
- Examples of autocoids:
    - **Biogenic amines:** Histamine, 5-hydroxytryptamine (5-HT or serotonin)
    - **Lipid-derived:** Prostaglandins, thromboxanes, leukotrienes
    - **Peptides:** Bradykinin, substance P
    - **Platelet activating factor (PAF)**
- Autocoid antagonists are drugs that inhibit their synthesis, release, or receptor-mediated actions, used in a wide range of clinical conditions.

Classification of Autocoids

Autocoids can be classified based on their chemical structure or origin:



A. Biogenic Amine Autocoids:

- Histamine
- 5-Hydroxytryptamine (Serotonin)

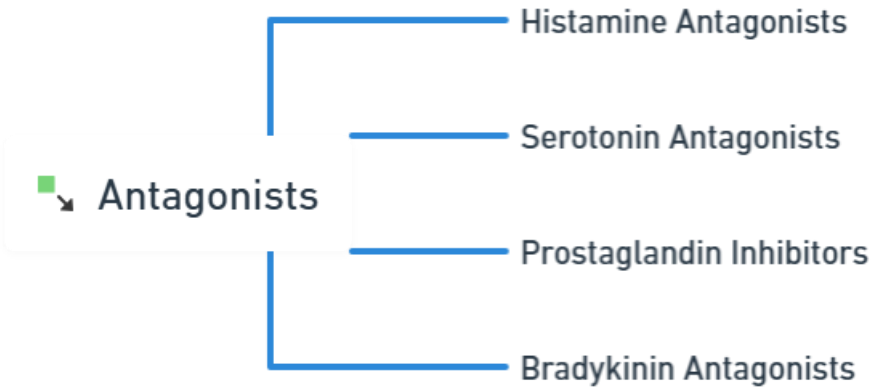
B. Lipid-Derived Autocoids:

- Prostaglandins (PGs)
- Thromboxanes (TXA_2)
- Leukotrienes (LTs)
- Platelet Activating Factor (PAF)

C. Peptide Autocoids:

- Bradykinin
- Substance P
- Vasoactive Intestinal Peptide (VIP)

Antagonists of Autocoids:



1. Histamine Antagonists (Antihistamines):

- H_1 receptor antagonists (e.g., diphenhydramine, loratadine)
- H_2 receptor antagonists (e.g., ranitidine, famotidine)

2. Serotonin Antagonists:

- 5-HT_3 antagonists (e.g., ondansetron)
- 5-HT_2 antagonists (e.g., cyproheptadine)

3. Prostaglandin Inhibitors:

- NSAIDs (e.g., aspirin, ibuprofen) – inhibit cyclooxygenase
- Leukotriene antagonists (e.g., montelukast)
- PAF antagonists (experimental)

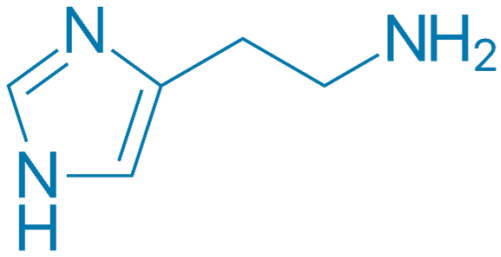
4. Bradykinin Antagonists:

- Icatibant (selective B_2 receptor antagonist)

Histamine

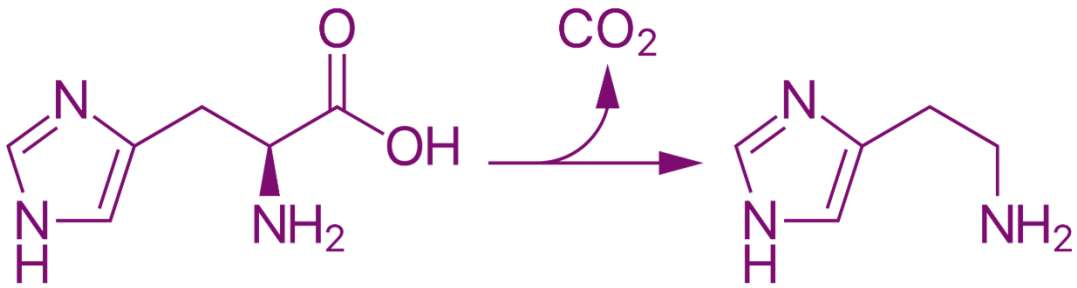
Introduction

- Histamine is a biologically active biogenic amine involved in:
  - Immune responses
  - Allergic reactions
  - Inflammation
  - Gastric acid secretion
  - Neurotransmission



Synthesis and Storage

- Synthesized from histidine by the enzyme histidine decarboxylase



- Stored in:
  - **Mast cells**
  - **Basophils**
  - **Certain neurons** (especially in the CNS)
  - **Enterochromaffin-like (ECL) cells** in the gastric mucosa

Triggers for Histamine Release

- IgE-mediated allergic reactions
- Mechanical or chemical injury
- Certain **drugs** that cause non-IgE mediated release:
  - **Morphine**
  - **Vancomycin**

- **Tubocurarine**

Histamine Receptors

Histamine exerts effects through four G-protein coupled receptors (GPCRs):

Receptor	Location	Major Functions
H_1	Smooth muscle, endothelium, brain	Vasodilation, bronchoconstriction, ↑ permeability, sensory nerve stimulation
H_2	Gastric parietal cells, heart, uterus	↑ Gastric acid secretion, ↑ heart rate, smooth muscle relaxation
H_3	CNS (presynaptic neurons)	↓ Release of neurotransmitters (modulation of CNS activity)
H_4	Bone marrow, immune cells	Chemotaxis and immune cell regulation

Mechanism of Action (Histamine Agonist Effects)

H_1 Receptor Activation

- Coupled to Gq protein
- Activates **phospholipase C (PLC)** → ↑ IP_3 and DAG → ↑ intracellular Ca^{2+}
- Effects:
  - Bronchoconstriction
  - Vasodilation (via NO)
  - Increased capillary permeability
  - Itching and pain via stimulation of sensory nerves

H_2 Receptor Activation

- Coupled to Gs protein
- Activates **adenylyl cyclase** → ↑ cAMP
- Effects:
  - Increased gastric acid secretion
  - Positive inotropic and chronotropic cardiac effects
  - Smooth muscle relaxation (e.g., uterus, bronchi)

Pharmacodynamics of Histamine

H_1 Receptor Effects

- Flushing, hypotension (vasodilation)
- Edema, wheal formation (↑ permeability)

- Bronchoconstriction
- Itching, pain
- CNS arousal or sedation

H_2 Receptor Effects

- Gastric acid secretion
- Increased heart rate and contractility
- Smooth muscle relaxation

Adverse Effects of Excess Histamine

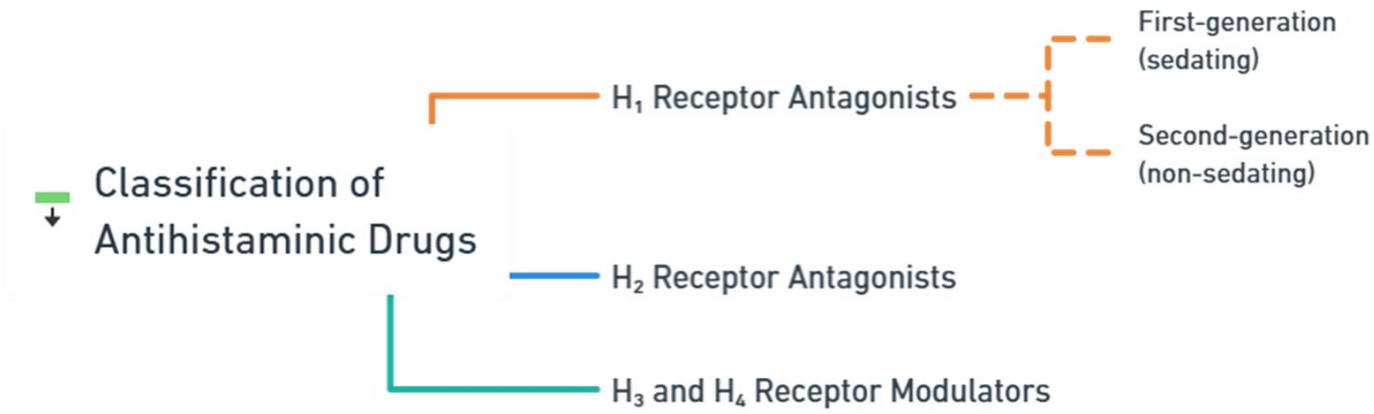
- Flushing
- Headache
- Hypotension
- Bronchospasm
- **Anaphylaxis** (massive histamine release from mast cells)

Antihistaminics

Definition

- Antihistamines are drugs that block the effects of histamine by acting as competitive antagonists or inverse agonists at histamine receptors (mainly H_1 and H_2).

Classification of Antihistaminic Drugs



1. H_1 Receptor Antagonists:

A. First-generation (sedating)

- Diphenhydramine
- Chlorpheniramine
- Hydroxyzine

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