**AUTOCOIDS**

*(LOCAL HORMONES)*

- Endogenous substances with biological activity.
- Local hormones
  1. Not released or stored in glands.
  2. Not circulated in blood.
  3. are formed at the site of action.
  4. Produce localized action.
AUTACOIDS

CLASSIFICATION

Biologically active amines:
histamine – serotonin

Lipid derived autacoids (Eicosanoids)
prostaglandins – leukotrienes – thromboxanes
Vasoactive polypeptides e.g.
kinins – Angiotensin – Endothelin-
Natriuretic peptide- Vasopressin
substance P

Endothelium derived autacoids
Nitric oxide
HISTAMINE

SYNTHESIS

Histamine decarboxylase

Histidine → Histamine

OCCURRENCE

Tissues exposed to external environment ( GIT, lung, skin, brain ) - stored in mast cells and basophiles.

METABOLISM

- Monoamine oxidase (MAO).
- Diamine oxidase or histaminase.
- Imidazole N-methyl transferase
RELEASE

Immunologic release:

mast cells sensitized by IgE attached to their surface membrane.

Non-Immunologic release (Drug-induced):

- morphine
- Curare
- apomorphine
- Chemical and physical injury of mast cells
Mechanism of action (H1– H2- H3)

**H1 receptors**
- coupled to phospholipase C (IP3& DAG)
- smooth muscles (contraction of bronchi, GIT & uterus except blood vessels).

**H2 receptors**
- Stimulate adenyl cyclase enzyme & increase cAMP
- **Heart** ( + ve inotropic & chronotropic effects)
- **Stomach** ( acid secretion).
H3 receptors
- G-protein –coupled
- presynaptic sites CNS & inhibit release of other neurotransmitters.

Pharmacological actions
- Contraction of smooth muscles (bronchi, uterus and GIT).
- CVS
  - Vasodilatation of BV
  - Increased capillary permeability (oedema)
  - Tachycardia : Cardiac stimulation (H2)
- Dilatation of cerebral vessels (headache, histamine cephalgia)

- **Exocrine glands:** stimulates gastric secretion.

- Stimulation of **sensory nerve endings** (pain & itching)

- **Skin:** Triple response

  - **Reddness** (vasodilatation of capillaries)
  - **Wheal** (oedema)
  - **Flare** (stimulation of sensory nerve endings).

- Release of catecholamines from adrenal medulla.
Histamine agonists
For diagnosis of phaeochromocytoma.

Histamine Antagonism
1. Mast cells stabilizers e.g. cromoglycate & corticosteroids.
2. Physiological antagonism by adrenaline
3. Receptors antagonists
   - H1- receptor blockers (antihistaminics-allergy)
   - H2- receptor blockers (peptic ulcer).
H1-receptor blockers
(Antihistaminics)

Mechanism of action
- They are competitive antagonists for H1 receptors.

Pharmacological effects
- **H1-receptor blockade**: they block histamine effects on smooth muscles and blood vessels.
- **Atropine like actions**: dry mouth, urinary retention, tachycardia (side effects).
- **Alpha-blocking activity** (postural hypotension).
- **Block serotonin receptors** as cyproheptadine
CNS

- Sedation
  - First generation produces sedation & hypnosis
  - Second generation have little or no sedative action.
- Antiemetic action (Motion sickness)
- Antiparkinsonian effects
Table 16-2. Some H₁ antihistaminic drugs in past or current clinical use.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Usual Adult Dose</th>
<th>Anti-Cholinergic Activity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST-GENERATION ANTIHISTAMINES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethanolamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbinoxamine (Clistin)</td>
<td>4–8 mg</td>
<td>+++</td>
<td>Slight to moderate sedation</td>
</tr>
<tr>
<td>Dimenhydrinate (salt of diphenhydramine (Dramamine)</td>
<td>50 mg</td>
<td>+++</td>
<td>Marked sedation; anti-motion sickness activity</td>
</tr>
<tr>
<td>Diphenhydramine (Benadryl, etc)</td>
<td>25–50 mg</td>
<td>+++</td>
<td>Marked sedation; anti-motion sickness activity</td>
</tr>
<tr>
<td>Doxylamine</td>
<td>1.25–25 mg</td>
<td>nd</td>
<td>Marked sedation; now available only in OTC “sleep aids”</td>
</tr>
<tr>
<td><strong>Ethylaminediamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrilamine (Neo-Antergan)</td>
<td>25–50 mg</td>
<td>+</td>
<td>Moderate sedation; component of OTC “sleep aids”</td>
</tr>
<tr>
<td>Tripelennamine (PBZ, etc)</td>
<td>25–50 mg</td>
<td>+</td>
<td>Moderate sedation</td>
</tr>
<tr>
<td><strong>Piperazine derivatives</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine (Atarax, etc)</td>
<td>15–100 mg</td>
<td>nd</td>
<td>Marked sedation</td>
</tr>
<tr>
<td>Cyclizine (Marezine)</td>
<td>25–50 mg</td>
<td>–</td>
<td>Slight sedation; anti-motion sickness activity</td>
</tr>
<tr>
<td>Meclizine (Bonine, etc)</td>
<td>25–50 mg</td>
<td>–</td>
<td>Slight sedation; anti-motion sickness activity</td>
</tr>
<tr>
<td><strong>Alkylamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brompheniramine (Dimetane, etc)</td>
<td>4–8 mg</td>
<td>+</td>
<td>Slight sedation</td>
</tr>
<tr>
<td>Chlorpheniramine (Chlor-Trimeton, etc)</td>
<td>4–8 mg</td>
<td>+</td>
<td>Slight sedation; common component of OTC “cold” medication</td>
</tr>
<tr>
<td><strong>Phenothiazine derivatives</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promethazine (Phenergan, etc)</td>
<td>10–25 mg</td>
<td>+++</td>
<td>Marked sedation; antiemetic</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyproheptadine (Periactin, etc)</td>
<td>4 mg</td>
<td>+</td>
<td>Moderate sedation; also has antiserotonin activity</td>
</tr>
</tbody>
</table>
First generation antihistaminics

Classifications

1. Ethanolamine:
   Diphenhydramine - Doxylamine (sedative-antiemetic)

2. Piperazine:
   Meclizine – cyclizine (antiemetic)

3. Phenothiazine:
   Promethazine (sedative - antiemetic)

4. Alkylamine: chlorpheniramine (cold/allergy, OTC)

5. Miscellaneous: Cyproheptadine
First generation antihistaminics

**Pharmacokinetics**
- Well absorbed orally,
- Short duration 3-6 hr
- Widely distributed,
- Penetrate BBB
- Metabolized in the liver.

**Side effects**
- Sedation and drowsiness
- Antimuscarinic effects
- Alpha blocking adverse effects
- Excitation in high doses in children
Second generation antihistaminics

Fexofenadine- Cetirizine, Loratidine-
Terfinadine, Astemizole - Acrivastine

Advantages of second generation

- Can not cross BBB
- No sedation
- Less atropine like actions
- Longer duration of action
- BUT More expensive
USES of Antihistaminics

- **Allergic reactions**
  - Rhinitis, hay fever, mild asthma, conjunctivitis, urticaria.
  - Chlorpheniramine
  - Second generation (mostly used)

- **Anti-emetic in motion sickness & Vestibular disturbances**
  - Dimenhydrinate – promethazine-cyclizine

- **Sedation** promethazine
H2 receptor antagonists

- Cimetidine – Ranitidine – Famotidine
- Inhibit gastric secretion
- Cytochrome p450 inhibitor (only cimetidine).
- Treatment of Peptic ulcer.
Serotonin  
( 5-Hydropxytryptamine, 5-HT )

**Synthesis**

- L-tryptophan by hydroxylation to give 5-hydroxy tryptophan, decarboxylated again to 5-HT.

- in enterochromaffin cells of GIT and in CNS.
Serotonin

Present in
- GIT (enterochromaffin cells)
- Platelets
- CNS (raphe nuclei of brain stem)
- Pineal gland, it acts as a precursor to melatonin.

Metabolism
- MAO into 5-hydroxyindole acetic acid (5-HIAA) which is excreted in urine.
- Urinary 5-HIAA is increased by carcinoid tumor.
Mechanism of Action:

5HT1 receptors inhibit adenylate cyclase → cAMP (CNS).

5HT2 receptors linked to PLC raising IP3 & DAG levels (smooth muscles-platelets – CNS).

5HT3 receptors linked to membrane ion channels (Sensory and enteric nerves & Area postrema).

5HT4 receptors ↑ cAMP (enteric N.S. – CNS, smooth muscles).

5HT 6, 7 & 8 unknown (CNS) (Figure 16-4)
<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>Distribution</th>
<th>Postreceptor Mechanism</th>
<th>Partially Selective Agonists</th>
<th>Partially Selective Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>Raphe nuclei, hippocampus</td>
<td>Multiple, Gi coupling dominates</td>
<td>8-OH-DPAT</td>
<td>WAY100635</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1B&lt;/sub&gt;</td>
<td>Substantia nigra, globus pallidus, basal ganglia</td>
<td>Gi, ↓ cAMP</td>
<td>CP93129</td>
<td></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1D,E&lt;/sub&gt;</td>
<td>Brain</td>
<td>Gi, ↓ cAMP</td>
<td>Sumatriptan</td>
<td></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1F&lt;/sub&gt;</td>
<td>Cortex, hippocampus</td>
<td>Gi, ↓ cAMP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1P&lt;/sub&gt;</td>
<td>Enteric nervous system</td>
<td>C&lt;sub&gt;B&lt;/sub&gt;, slow EPSP</td>
<td>5-Hydroxyindalpine</td>
<td>Renzapride</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>Platelets, smooth muscle, cerebral cortex, skeletal muscle</td>
<td>Gi, ↑ IP&lt;sub&gt;3&lt;/sub&gt;</td>
<td>α-Methyl-5-HT</td>
<td>Ketanserin</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2B&lt;/sub&gt;</td>
<td>Stomach fundus</td>
<td>Gi, ↑ IP&lt;sub&gt;3&lt;/sub&gt;</td>
<td>α-Methyl-5-HT</td>
<td>SB204741</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt;</td>
<td>Choroid, hippocampus, substantia nigra</td>
<td>Gi, ↑ IP&lt;sub&gt;3&lt;/sub&gt;</td>
<td>α-Methyl-5-HT</td>
<td>Mesulergine</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Area postrema, sensory and enteric nerves</td>
<td>Receptor is a Na&lt;sup&gt;+&lt;/sup&gt;-K&lt;sup&gt;+&lt;/sup&gt; ion channel</td>
<td>2-Methyl-5-HT, m-chlorophenylbiguanide</td>
<td>Tropisetron, ondansetron, granisetron</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CNS and myenteric neurons, smooth muscle</td>
<td>Gi, ↑ cAMP</td>
<td>5-Methoxytryptamine, renzapride, metoclopramide</td>
<td></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;5A,B&lt;/sub&gt;</td>
<td>Brain</td>
<td>↓ cAMP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;6,7&lt;/sub&gt;</td>
<td>Brain</td>
<td>Gi, ↑ cAMP</td>
<td>Clozapine (5-HT&lt;sub&gt;6&lt;/sub&gt;)</td>
<td></td>
</tr>
</tbody>
</table>

8-OH-DPAT = 8-Hydroxy-2-(di-n-propylamino)tetralin; CP93129 = 5-Hydroxy-3(4,1,2,5,6-tetrahydropyridyl)-4-azaindole; SB204741 = N-(1-methyl-5-indolyl)-N'-(3-methyl-5-isothiazolyl)urea; WAY100635 = N-tert-Butyl 3-4-(2-methoxyphenyl)piperazin-1-yl-2-phenylpropanamide
Pharmacological Actions

- **Vasoconstriction** of renal, pulmonary & cerebral vessels.
- **Vasodilatation** of skeletal muscles & Heart BV
- **Weak inotropic and chronotropic effects** blunted by effects on the baroreceptors, chemoreceptors and vagal efferents that result in bradycardia.
- **Smooth Muscle**: contraction of smooth muscle (GIT, bronchial tree and uterus, 5-HT4).
- **Weak bronchoconstriction**
Platelets aggregation

Hypotension -hypertension-hypotension

Hypotension due to

activation of chemoreceptor nerve endings

direct vasoconstriction.

Hypotension due to skeletal vasodilatation.
- Stimulation of sensory nerve endings (pain & itching sensation).

**CNS**
- Control mood, temp
- Inhibit appetite (anorexigenic effect)
- Anxiety
- Induction of vomiting (5HT3).
- Diseases migraine, carcinoid syndrome, anxiety
SEROTONIN AGONISTS

Sumartiptan
- 5HT1d agonist cranial vessels vasoconstriction.
- It has no CNS effects.
- Treat migraine attacks

Buspirone and Ipsapirone
- Partial 5HT1A agonists.
- Anxiolytics in anxiety disorders.

Tegaserod
- Partial 5HT5 agonist
- Used for irritable bowel syndrome with constipation.
Dexfenfluramine
- Stimulate 5-HT release.
- appetite suppressant (anorexigenic action)

Urapidil
- 5-HT1A agonists
- Decrease centrally sympathetic tone and increase vagal tone
- Used to control blood pressure

5-HT reuptake inhibitors
- Fluoxetine- paroxetine. They are useful antidepressants
SEROTONIN ANTAGONISTS

Block of Synthesis
Pharachlorophenylalanine (PCPA).

Block of Storage: Resepine.

Receptors Blockers:
Cyproheptadine (Periactin):
- 5-HT2 antagonist.
- Histamine H1-and muscarinic antagonists.
- Carcinoid tumors.

Pizotifen (Mosegor):
- Similar to cyproheptadine.
- Appetite stimulation.

Methysergide (Deseril):
- 5-HT2 antagonist
- Migraine prophylaxis – carcinoid tumors
Ondansetron and Granisetron
- 5HT3 antagonists
- Block vomiting centers and CTZ
- Antiemetics

Metoclopramide
- blocks 5HT3 receptors (antiemetic action)
- blocks dopamine receptors (antiemetic action)
- stimulates cholinergic system (prokinetic)

Ketanserin
- blocks 5HT2, H1, alpha 1 receptors
- Hypertension
Carcinoid tumor
Malignant tumor in enterochromaffin cells of GIT.

Features
- Bronchospasm
- GIT: diarrhea-colics
- Flushing of the face

Diagnosis
- High plasma level of serotonin
- High 5-HIAA in urine

Treatment
Cyproheptadine- Methysergide.
Ergot alkaloids

- Formed by fungus
- Several receptors (Dopamine, 5-HT, α-receptors).

Pharmacological actions

I. CNS
1. Stimulate Dopamine receptors & decrease prolactin and parkinsonism.
2. Stimulation of cerebral vessels (5-HT2).

II. Smooth muscles
1. Vasoconstriction of blood vessels
2. Contraction of uterus
3. Nausea, vomiting, diarrhea
Table 16-5. Effects of ergot alkaloids at several receptors.¹

<table>
<thead>
<tr>
<th>Ergot Alkaloid</th>
<th>α Adrenoceptor</th>
<th>Dopamine Receptor</th>
<th>Serotonin Receptor (5-HT₂)</th>
<th>Uterine Smooth Muscle Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>−</td>
<td>+++</td>
<td>−</td>
<td>0</td>
</tr>
<tr>
<td>Ergonovine</td>
<td>+</td>
<td>+</td>
<td>− (PA)</td>
<td>+++</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>− (PA)</td>
<td>0</td>
<td>+ (PA)</td>
<td>+++</td>
</tr>
<tr>
<td>Lysergic acid diethylamide (LSD)</td>
<td>0</td>
<td>+++</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Methysergide</td>
<td>+/-</td>
<td>+/-</td>
<td>− (PA)</td>
<td>+/0</td>
</tr>
</tbody>
</table>

¹Agonist effects are indicated by +, antagonist by −, no effect by 0. Relative affinity for the receptor is indicated by the number of + or − signs. PA means partial agonist (both agonist and antagonist effects can be detected).
Types & uses

- Migraine treatment: Ergotamine & dihydroergotamine (5HT1 & 5HT2)
- Migraine prophylaxis: Methysergide (5HT2)
- Postpartum hemorrhage: Ergometrine (Ergonovine)
- Endocrine disorders (hyperprolactinemia) - Parkinsonism
  Bromocriptine (dopamine agonist).
Side Effects

A condition called Ergotism

- Nausea, vomiting, diarrhea
- Severe vasospasm (gangrene)
- Confusion, weak pulse