# 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

Histidine —(Histamine decarboxylase)→ 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 $H_1$ antihistaminic drugs in past or current clinical use.

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

# 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-Hydrpxytryptamine, 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** unkown ( CNS) (Figure 16-4)

**Table 16–3.** Serotonin receptor subtypes.

| Receptor Subtype | Distribution | Postreceptor Mechanism | Partially Selective Agonists | Partially Selective Antagonists |
|---|---|---|---|---|
| 5-$HT_{1A}$ | Raphe nuclei, hippocampus | Multiple, $G_i$ coupling dominates | 8-OH-DPAT | WAY100635 |
| 5-$HT_{1B}$ | Substantia nigra, globus pallidus, basal ganglia | $G_i$, ↓ cAMP | CP93129 | |
| 5-$HT_{1Da,b}$ | Brain | $G_i$, ↓ cAMP | Sumatriptan | |
| 5-$HT_{1E}$ | Cortex, putamen | $G_i$, ↓ cAMP | | |
| 5-$HT_{1F}$ | Cortex, hippocampus | $G_i$, ↓ cAMP | | |
| 5-$HT_{1P}$ | Enteric nervous system | $G_o$; slow EPSP | 5-Hydroxyindalpine | Renzapride |
| 5-$HT_{2A}$ | Platelets, smooth muscle, cerebral cortex, skeletal muscle | $G_q$, ↑ $IP_3$ | α-Methyl-5-HT | Ketanserin |
| 5-$HT_{2B}$ | Stomach fundus | $G_q$, ↑ $IP_3$ | α-Methyl-5-HT | SB204741 |
| 5-$HT_{2C}$ | Choroid, hippocampus, substantia nigra | $G_q$, ↑ $IP_3$ | α-Methyl-5-HT | Mesulergine |
| 5-$HT_3$ | Area postrema, sensory and enteric nerves | Receptor is a $Na^+$-$K^+$ ion channel | 2-Methyl-5-HT, *m*-chlorophenylbiguanide | Tropisetron, ondansetron, granisetron |
| 5-$HT_4$ | CNS and myenteric neurons, smooth muscle | $G_s$, ↑ cAMP | 5-Methoxytryptamine, renzapride, metoclopramide | |
| 5-$HT_{5A,B}$ | Brain | ↓ cAMP | | |
| 5-$HT_{6,7}$ | Brain | $G_s$, ↑ cAMP | | Clozapine (5-$HT_7$) |

8-OH-DPAT = 8-Hydroxy-2-(di-*n*-propylamine)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:**

**Cyprohepatadine ( 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]

| Ergot Alkaloid | α Adrenoceptor | Dopamine Receptor | Serotonin Receptor ($5\text{-}HT_2$) | Uterine Smooth Muscle Stimulation |
|---|---|---|---|---|
| Bromocriptine | – | +++ | – | 0 |
| Ergonovine | + | + | – (PA) | +++ |
| Ergotamine | – – (PA) | 0 | + (PA) | +++ |
| Lysergic acid diethylamide (LSD) | 0 | +++ | – – ++ in CNS | + |
| Methysergide | +/0 | +/0 | – – – (PA) | +/0 |

[1]Agonist 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