

AUTACOIDS

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AUTACOIDS

Endogenous substances with complex physiologic and pathphysiologic functions; commonly understood to include histamine, serotonin, prostaglandins, and vasoactive peptides.

Local hormones

Histamine

- Occurs in plants, animals, venoms, and stinging secretions.
- Formed from l-histidine.
- Mediator of immediate allergic , and inflammatory reactions.
- Plays only a modest role in anaphylaxis.
- Gastric acid secretion.
- Neurotransmission.

Histamine

- **Stored in granules in mast cells and basophils, and inactivated.**
- **Immunologic Release:**
 - **IgE and antigen interaction causes explosive degranulation and release of histamine, ATP, and other mediators.**
- **Chemical and Mechanical Release:**
 - **Drugs like morphine and tubocurarine.**

Molecular Actions of Histamine

- **G Protein Coupled Receptors:**
- **H₁, H₂, H₃, H₄ types, no subfamilies.**
- **Activation of H₁ receptors (in endothelium, smooth muscle cells, and nerve endings), elicits inositol triphosphate(IP₃).**
- **Activation of H₂ receptors(in gastric mucosa, cardiac muscle, and some immune cells), increases cAMP**

Histamine Receptors

G-protein coupled receptors (GPCR)

- H₁:** smooth muscle, endothelium, brain (post-synaptic)
- H₂:** gastric mucosa, heart, mast cells, brain (post-synaptic)
- H₃:** presynaptic, mostly in neural tissue
- H₄:** bone marrow & blood WBC

Pharmacologic Effects of Histamine

- Satiety effect
- Decrease BP and increase HR.
- Constricts bronchial muscle.
- Stimulates GI smooth muscle.
- Stimulates gastric acid secretion.
- ***Triple Response***: intradermal injection causes red spot, edema, and flare response.
- Pain sensation.

Histamine Antagonism

- **Physiologic Antagonism:**
 - Epinehrine
- **Release Inhibitors:**
 - Cromolyn
 - Nedocromil
- **Receptor Antagonists:**
 - H₁ antagonists
 - H₂ antagonists

H1 Receptor Antagonists

- Reversible competitive binding to H₁ receptors.
- Known long time ago, 60 years.
- Used in the treatment of allergy.
- Available without a prescription, both alone, or in combination as 'cold preparations'' and 'sleep aids''

H1 Receptor Antagonists

- **First Generation:**
 - Strong sedatives because they can cross BBB.
 - Have autonomic blocking effects
- **Second Generation:**
 - Less lipid soluble, so not sedative.

Pharmacodynamics of H1 Antagonists

- **Sedation:**
 - **Very common with first generation agents.**
 - **Varies among agents and patients.**
 - **No abuse potential.**
 - **Can cause stimulation and convulsions at high doses.**
- **Antinausea and antiemetic actions**
- **Antiparkinsonism effects**
- **Anticholinergic effects.**
- **Alpha blocking effect**
- **Serotonin blocking effect**
- **Local anesthesia**

ANTI-HISTAMINE

Dosing
hrs

Actions

Ethanolamines

Diphenhydramine (*Benadryl*)

4-8

Strong Sedative
Strong anti-cholinergic
Anti-motion sickness

Ethylaminediamines

Pyrilamine (*Neo-Antergan*)

4-6

Mild anti-cholinergic
Moderate sedative
GI side effects

Piperazines

Hydroxyzine (*Atarax*)

Cyclizine (*Merezine*)

4-8

24

Strong sedative; anxiolytic
Mild sedative
Anti-motion sickness

Alkylamines

Brompheniramine (*Dimetane*)

Chlorpheniramine (*ChlorTrimeton*)

4-6

Mild anti-cholinergic
Mild sedative
In OTC Cold preparations

ANTI-HISTAMINE

Dosing
hrs

Actions

Phenothiazines

Promethazine (*Phenergan*)

6-24

Strong Sedative
Strong Anti-cholinergic
Anti-Emetic

Miscellaneous

Cyproheptadine (*Periactin*)

8

Moderate Sedative
Mild Anti-cholinergic
Anti-serotonergic

Clinical uses of H1 Antagonists



- **Allergic reactions:**
 - More effective when given before exposure.
 - Sedative effect reduces awareness of itching.
 - Local application may induce allergy by itself.
- **Motion Sickness and Vestibular Disturbances:**
Menier's Syndrome.
- **Nausea and vomiting of Pregnancy (*Morning Sickness*):**
 - Teratogenic in rodents.

H2 Antagonists

- Breakthrough treatment for peptic ulcer disease(1972).
- Do not completely abolish acid secretion.
- Proton pump inhibitors are more effective.
- Cimetidine.
- Ranitidine.
- Famotidine.
- Naziditine.

Serotonin and 5-Hydroxytryptamine

- **Serotonin: a vasoconstrictor released from the blood clot.**
- **Enteramine: a smooth muscle stimulant found in intestinal mucosa.**
- **5-Hydroxytryptamine(synthesized in 1951)**

Serotonin and 5-Hydroxytryptamine

- **Widely distributed in nature, found in plant (Banana) and animal tissues, venoms, and stings.**
- **Synthesized from L-tryptophan.**
- **Stored or rapidly inactivated by MAO.**
- **90% is found in the enterochromaffin cells of the GIT.**
- **Also found in platelets, enteric nervous system, nerve endings, and brain.**
- **Involved in mood, sleep, appetite, temperature control, and pain perception.**
- **Involved in depression, anxiety, migraine,**

Serotonin(5HT) Receptors

- 7 subtypes (5HT₁ to 5HT₇)
- 5HT₃: member of nicotinic/GABA_A family of Na⁺/K⁺ channels
- All others: GPCR

Subtype	Tissue Distribution	Signaling Mechanism	Agonist	Antagonist
5-HT _{1A}	CNS	Gi, ↓cAMP	Sumatriptan	
5-HT _{1B}				
5-HT _{1D}				
5-HT _{1E} 5HT- _{1F} 5HT- _{1P}	Enteric NS	Go, slow EPSP		
5-HT _{2A}	Platelets, smooth muscle, CNS	Gq, ↑IP3		Ketanserin
5-HT _{2B} 5-HT _{2C}	Stomach CNS			
5-HT ₃	CNS, sensory & enteric nerves	Na ⁺ /K ⁺ channel		Ondansetron, Granisetron Tropisetron
5-HT ₄	CNS & myenteric neurons, smooth muscle	Gs, ↑cAMP	Cisapride	
5-HT ₅	CNS	↓cAMP		
5-HT _{6,7}	CNS	Gs, ↑cAMP		Clozapine

Pharmacologic Effects of Serotonin

- **Nervous System:**
 - Melatonin
 - Chemoreceptor Reflex(*Bezold-Jarish Reflex*): activation of 5-HT₃ receptors in coronary arteries, leads to hypotension and bradycardia.
- **Respiratory System:**
 - Bronchoconstriction and hyperventilation.
- **Cardiovascular System:**
 - Vasoconstriction.
 - Vasodilation in skeletal muscles and coronary arteries. Intact endothelium is required
 - Platelets aggregation.

Pharmacologic Effects of Serotonin

- **GIT:**
 - Stimulation and diarrhea.
 - *Carcinoid Syndrome*: due to a tumor of the enterochromaffin cells.
- **Skeletal Muscle:**
 - *Serotonin Syndrome*:
 - Potentially fatal .
 - Skeletal muscle contraction and hyperthermia
 - Due to excess serotonergic activity.
 - Predictable, not idiosyncratic.

Clinical Uses of Serotonin Agonists

- **Serotonin:**
 - Has no clinical application.
- **Buspirone:**
 - 5HT_{1A} agonist, anxiolytic, nonsedating.
- **Triptans:**
 - 5HT_{1D/1B} agonists
 - First line drugs for migraine headache.
- **Cisapride:**
 - 5HT₄ agonist used only in gastroesophageal reflux.
- **Tagaserod:**
 - 5HT₄ agonist
- **Fluoxetine:**
 - SSRI, used in depression.

Serotonin Antagonists

- **Phenoxybenzamine:**
 - An alpha blocker
- **Cyproheptadine:**
 - 5HT₂ and H₁ blocker.
 - Useful in carcinoid and serotonin syndromes.
- **Ketanserine:**
 - 5HT₂ blocker, antihypertensive agent.
- **Ritanserine:**
 - 5HT₂ blocker, prevents platelets sggregation.
- **Ondansetron:**
 - 5HT₃ blocker, used to prevent nausea and vomiting of cancer chemotherapy.