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:
- H 1, 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)

H_1: smooth muscle, endothelium, brain (post-synaptic)

H_2: gastric mucosa, heart, mast cells, brain (post-synaptic)

H_3: presynaptic, mostly in neural tissue

H_4: 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.**

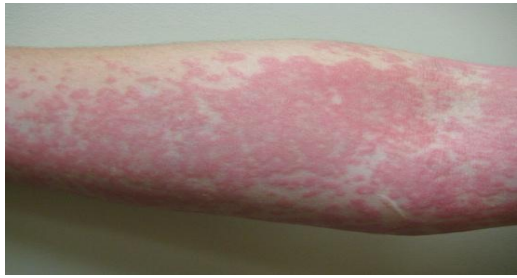
Pharmacodynamics of H1 Antagonists

- **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**

ANTIHISTAMINE	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

ANTIHISTAMINE	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 vsoconstrictor 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 ($5HT_1$ to $5HT_7$)**
- **$5HT_3$: member of nicotinic/$GABA_A$ family of Na^+/K^+ channels**
- **All others: GPCR**

Subtype	Tissue Distribution	Signaling Mechanism	Agonist	Antagonist
$5\text{-}HT_{1A}$	CNS	Gi,↓cAMP		
$5\text{-}HT_{1B}$			Sumatriptan	
$5\text{-}HT_{1D}$			Sumatriptan	
$5\text{-}HT_{1E}$				
$5HT\text{-}_{1F}$				
$5HT\text{-}_{1P}$	Enteric NS	Go, slow EPSP		
$5\text{-}HT_{2A}$	Platelets, smooth muscle, CNS	Gq,↑IP3		Ketanserin
$5\text{-}HT_{2B}$	Stomach			
$5\text{-}HT_{2C}$	CNS			
$5\text{-}HT_{3}$	CNS, sensory & enteric nerves	Na^+/K^+ channel		Ondansetron, Granisetron Tropisetron
$5\text{-}HT_{4}$	CNS & myenteric neurons, smooth muscle	Gs,↑cAMP	Cisapride	
$5\text{-}HT_{5}$	CNS	↓cAMP		
$5\text{-}HT_{6,7}$	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 contractiona nd hyperthermia**
    - **Due to excess serotnergic activity.**
    - **Predictable, not idiosyncratic.**

Clinical Uses of Serotonin Agonists

- **Serotonin:**
  - Has no clinical application.
- **Buspirone:**
  - 5HT1A agonist, anxiolytic, nonsedating.
- **Triptans:**
  - 5HT1D/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.**