AUTACOIDS

Munir Gharibeh, MD, PhD, MHPE
Faculty of Medicine, The University of Jordan
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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)

$H_1$: 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
<table>
<thead>
<tr>
<th>ANTIHISTAMINE</th>
<th>Dosing hrs</th>
<th>Actions</th>
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<tbody>
<tr>
<td><strong>Ethanolamines</strong></td>
<td></td>
<td></td>
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<tr>
<td>Diphenhydramine (<em>Benadryl</em>)</td>
<td>4-8</td>
<td>Strong Sedative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strong anti-cholinergic</td>
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<tr>
<td></td>
<td></td>
<td>Anti-motion sickness</td>
</tr>
<tr>
<td><strong>Ethylaminediethamines</strong></td>
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<tr>
<td>Pyrilamine (<em>Neo-Antergan</em>)</td>
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<td>Mild anti-cholinergic</td>
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<tr>
<td></td>
<td></td>
<td>Moderate sedative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI side effects</td>
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<tr>
<td><strong>Piperazines</strong></td>
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<tr>
<td><em>Hydroxyzine</em> (<em>Atarax</em>)</td>
<td>4-8</td>
<td>Strong sedative; anxiolytic</td>
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<td>Cyclizine (<em>Merezine</em>)</td>
<td>24</td>
<td>Mild sedative</td>
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<tr>
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<td></td>
<td>Anti-motion sickness</td>
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<tr>
<td><strong>Alkylamines</strong></td>
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<tr>
<td>Brompheniramine (<em>Dimetane</em>)</td>
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<td>Mild anti-cholinergic</td>
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<tr>
<td>Chlorpheniramine (<em>ChlorTrimeton</em>)</td>
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<td>Mild sedative</td>
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<tr>
<td></td>
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<td>In OTC Cold preparations</td>
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<tr>
<td>Phenothiazines</td>
<td>Dosing hrs</td>
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<tr>
<td>---------------------</td>
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<td>----------------------------------</td>
</tr>
<tr>
<td>Promethazine (Phenergan)</td>
<td>6-24</td>
<td>Strong Sedative</td>
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<td></td>
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<td>Strong Anti-cholinergic</td>
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<td></td>
<td></td>
<td>Anti-Emetic</td>
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<tr>
<td>Miscellaneous</td>
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<tr>
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<td>Anti-serotonergic</td>
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</table>
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.
Serothonin 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/GABAₐ family of Na⁺/K⁺ channels
- All others: GPCR
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Tissue Distribution</th>
<th>Signaling Mechanism</th>
<th>Agonist</th>
<th>Antagonist</th>
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<td>Gi,↓cAMP</td>
<td>Sumatriptan</td>
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<td>Go, slow EPSP</td>
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<td>Na&lt;sup&gt;+&lt;/sup&gt;/K&lt;sup&gt;+&lt;/sup&gt; channel</td>
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<td>5-HT&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CNS &amp; myenteric neurons, smooth muscle</td>
<td>Gs,↑cAMP</td>
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<td>CNS</td>
<td>Gs, ↑cAMP</td>
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</table>
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 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 aggregation.

- **Ondansetron:**
  - 5HT3 blocker, used to prevent nausea and vomiting of cancer chemotherapy.