AUTACOIDS

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AUTACOIDS

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

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. Two types of release:
- **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

TABLE 16–1 Histamine receptor subtypes.

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists or Inverse Agonists
H_1	Smooth muscle, endothelium, brain	G_q ↑ IP_3, DAG	Histaprodifen	Mepyramine,[1] triprolidine, cetirizine
H_2	Gastric mucosa, cardiac muscle, mast cells, brain	G_s ↑ cAMP	Amthamine	Cimetidine,[1] ranitidine,[1] tiotidine
H_3	Presynaptic autoreceptors and heteroreceptors: brain, myenteric plexus, other neurons	G_i ↓ cAMP	*R*-α-Methylhistamine, imetit, immepip	Thioperamide,[1] iodophenpropit, clobenpropit,[1] tiprolisant[1]
H_4	Eosinophils, neutrophils, CD4 T cells	G_i ↓ cAMP	Clobenpropit, imetit, clozapine	Thioperamide[1]

[1] Inverse agonist.

cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP_3, inositol triphosphate.

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 Antagonists

- Physiologic Antagonists:
  - 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(OTC), alone, or in combination as ‘cold preparations” and ‘sleep aids”

H1 Receptor Antagonists

- **First Generation:**
  - Strong sedatives because they can cross BBB. Dangers???.
  - Examples: Diphenhydramine, Chlorpheneramine
  - Have autonomic(α &M blocking effects
- **Second Generation:**
  - Less lipid soluble, so no sedative activity.
  - Examples: Fexofenadine, Loratidine, Cetrizine

Pharmacodynamics of H1 Antagonists

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

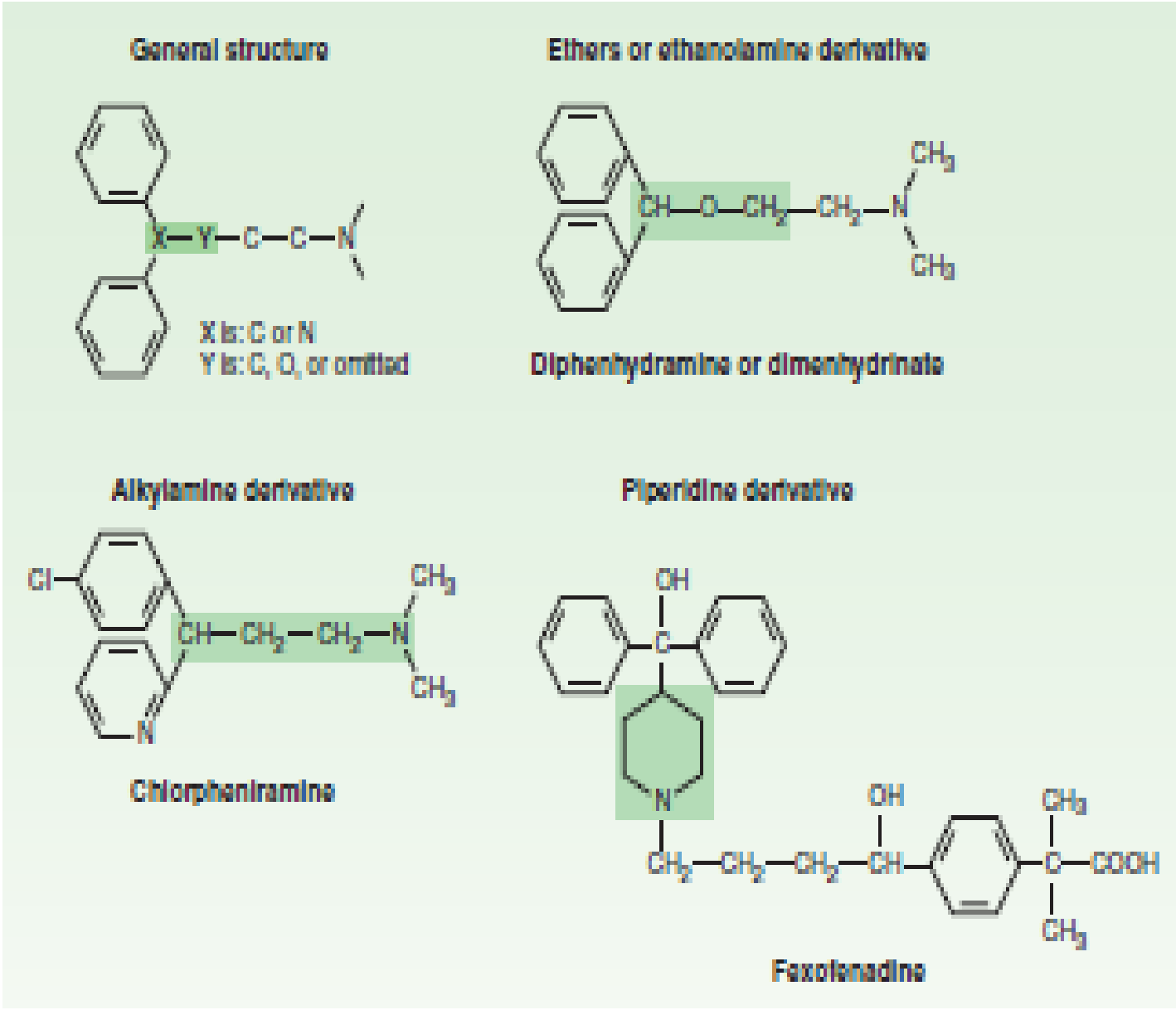

FIGURE 16–1 General structure of H_1-antagonist drugs and examples of the major subgroups. Chemical subgroups are indicated by shading.

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(40-60%).
- Replaced by proton pump inhibitors(100% inhibition).
- 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,

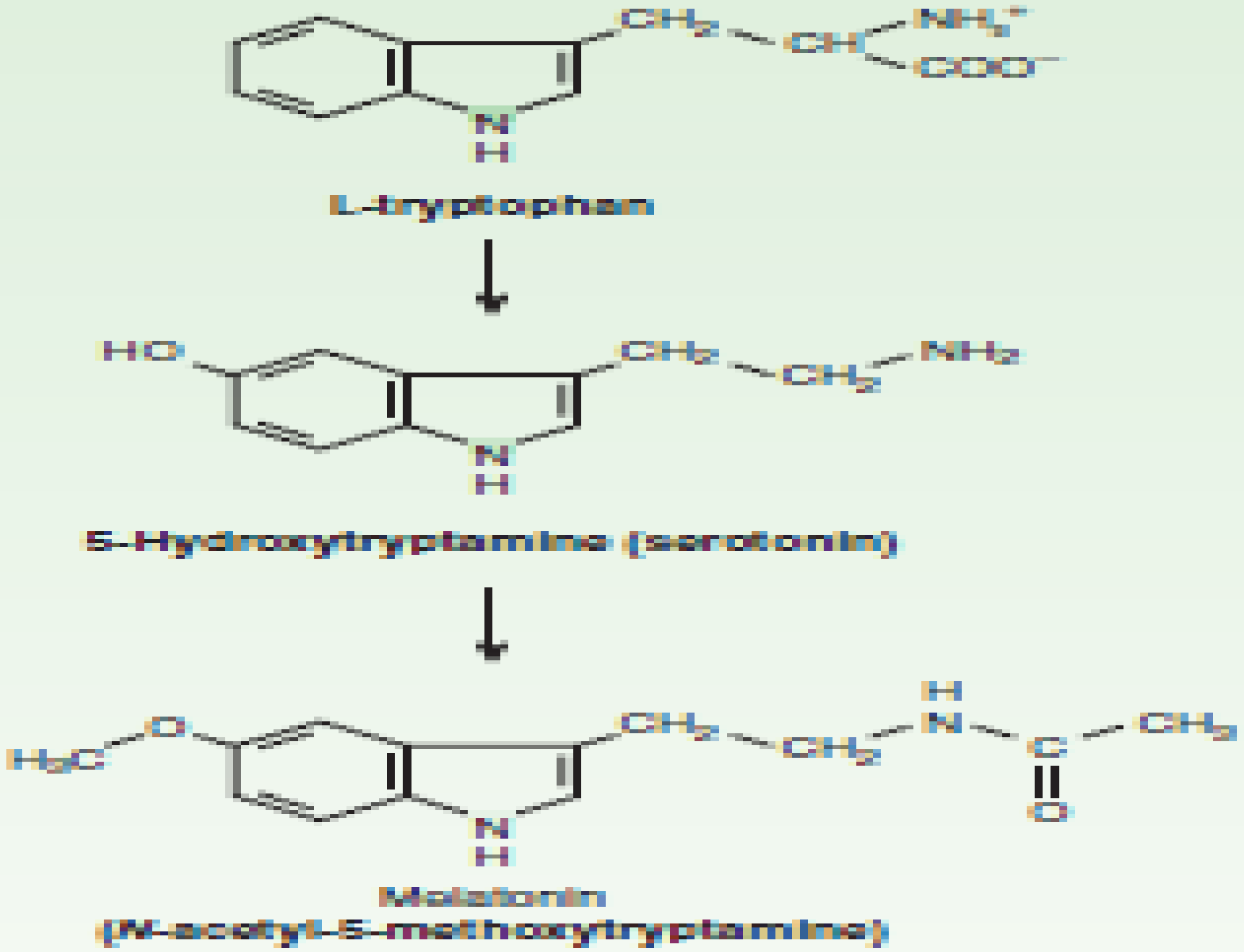

FIGURE 16—2 Synthesis of serotonin and melatonin from L-tryptophan.

TABLE 16–3 Serotonin receptor subtypes currently recognized. (See also Chapter 21.)

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-HT_{1A}	Raphe nuclei, hippocampus	G_i, ↓ cAMP	8-OH-DPAT,[1] repinotan	WAY100635[1]
5-HT_{1B}	Substantia nigra, globus pallidus, basal ganglia	G_i, ↓ cAMP	Sumatriptan, L694247[1]	
5-HT_{1D}	Brain	G_i, ↓ cAMP	Sumatriptan, eletriptan	
5-HT_{1E}	Cortex, putamen	G_i, ↓ cAMP		
5-HT_{1F}	Cortex, hippocampus	G_i, ↓ cAMP	LY334864[1]	
5-HT_{1P}	Enteric nervous system	G_s, slow EPSP	5-Hydroxyindalpine	Renzapride
5-HT_{2A}	Platelets, smooth muscle, cerebral cortex	G_q, ↑ IP_3	α-Methyl-5-HT, DOI[1]	Ketanserin
5-HT_{2B}	Stomach fundus	G_q, ↑ IP_3	α-Methyl-5-HT, DOI[1]	RS127445[1]
5-HT_{2C}	Choroid, hippocampus, substantia nigra	G_q, ↑ IP_3	α-Methyl-5-HT, DOI,[1] lorcaserin	Mesulergine
5-HT_3	Area postrema, sensory and enteric nerves	Receptor is a Na^+/K^+ ion channel	2-Methyl-5-HT, m-chlorophenylbiguanide	Granisetron, ondansetron, others
5-HT_4	CNS and myenteric neurons, smooth muscle	G_s, ↑ cAMP	BIMU8,[1] renzapride, metoclopramide	GR113808[1]
5-$HT_{5A,B}$	Brain	↓ cAMP		
5-$HT_{6,7}$	Brain	G_s, ↑ cAMP		Clozapine (5-HT_7)

[1]Research agents; for chemical names see Alexander SPH, Mathie A, Peters JA: Guide to receptors and channels (GRAC). Br J Pharmacol 2009;158 (Suppl 1):S12.

cAMP, cyclic adenosine monophosphate; EPSP, excitatory postsynaptic potential; IP_3, inositol triphosphate.

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:*
  - Due to excess serotnergic activity.
  - Potentially fatal .
  - Skeletal muscle contraction and hyperthermia
  - Predictable, not idiosyncratic.

Clinical Uses of Serotonin Agonists

- **Serotonin:**
  - Has no clinical application.
- **Buspirone:**
  - 5HT1A agonist, anxiolytic, nonsedating.
- **Triptans: e.g. Sumatryptan**
  - 5HT1D/1B agonists
  - First line drugs for migraine headache.
- **Cisapride:**
  - 5HT4 agonist used only in gastroesophageal reflux.
- **Tagaserod:**
  - 5HT4 agonist
- **Fluoxetine:**
  - SSRI, widely used in depression.

Serotonin Antagonists

Phenoxybenzamine:

- An old alpha blocker, but also 5HT blocker.

Cyproheptadine:

- 5HT2 and H1 blocker.
- Useful in carcinoid and serotonin syndrome.

Ketanserine:

- 5HT2 blocker, antihypertensive agent.

Ritanserine:

- 5HT2 blocker, prevents platelets sggregation.

Ondansetron:

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