Autacoids & Related Drugs

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Reference

Basic & Clinical Pharmacology

BG Katzung, SB Masters, AJ Trevor

McGraw Hill LANGE

12th edition pp 273-287, or 13th edition pp 271-286

Autacoids

- **Local hormones, often released locally.**
- **Have complex physiologic and pathologic effects through multiple receptor subtypes.**
- **Include histamine, serotonin (5-hydroxytryptamine), endogenous peptides, prostaglandins, leukotrienes, platelet-activating factor, kinins, cytokines and many others.**

Histamine

- **It is an important mediator of immediate allergic and inflammatory reaction, with a modest role in anaphylaxis.**
- **It induces gastric acid secretion.**
- **It functions as a neurotransmitter and neuromodulator.**
- **It may play a role in immune functions and chemotaxis of white blood cells.**

Histamine

Pharmacokinetics:

- Occurs in plants, animal tissues, venoms and sting secretions.
- Formed by decarboxylation of the amino acid L-histidine by histidine decarboxylase.
- Once formed, it is either stored or rapidly inactivated, very little is excreted unchanged.
- Most tissue histamine is sequestered and bound in granules in mast cells and basophiles.

Histamine

- **Histamine content of many tissues is directly related to their mast cell content.**
- **The bound form of histamine is biologically inactive.**
- **Mast cells are especially rich at sites of potential tissue injury — nose, mouth, and feet; internal body surfaces; and blood vessels, particularly at pressure points and bifurcations.**

Histamine

- **Neoplasms associated with increased number of mast cells and basophiles (systemic mastocytosis, urticaria pigmentosa, gastric carcinoid, and occasionally myelogenous leukemia) have increased excretion of histamine and its metabolites.**

Histamine

Non-mast cell histamine:

- **In the brain, it functions as a neurotransmitter, and plays a role in neuroendocrine control, cardiovascular regulation, thermal and body weight regulation, and sleep and arousal.**
- **In enterochromaffin-like (ECL) cells of the fundus of the stomach, it is involved in activation of the acid-producing parietal cells of the mucosa.**

Histamine

Storage and Release:

1. Immunologic release:

- Accounts for most pathophysiologic mechanism of mast cell and basophil histamine release.
- Antigen interaction with IgE attached to cell surface leads to degranulation of the cells releasing histamine, ATP and others.
- Requires energy and Ca^{2+}.

Histamine

- **IgG- and IgM-mediated immune reactions that activate the complement cascade also release histamine from mast cells and basophiles.**
- **Negative feedback control of histamine is mediated by histamine itself through H_2 receptors. Occurs in basophiles and skin mast cells but not in lung mast cells.**

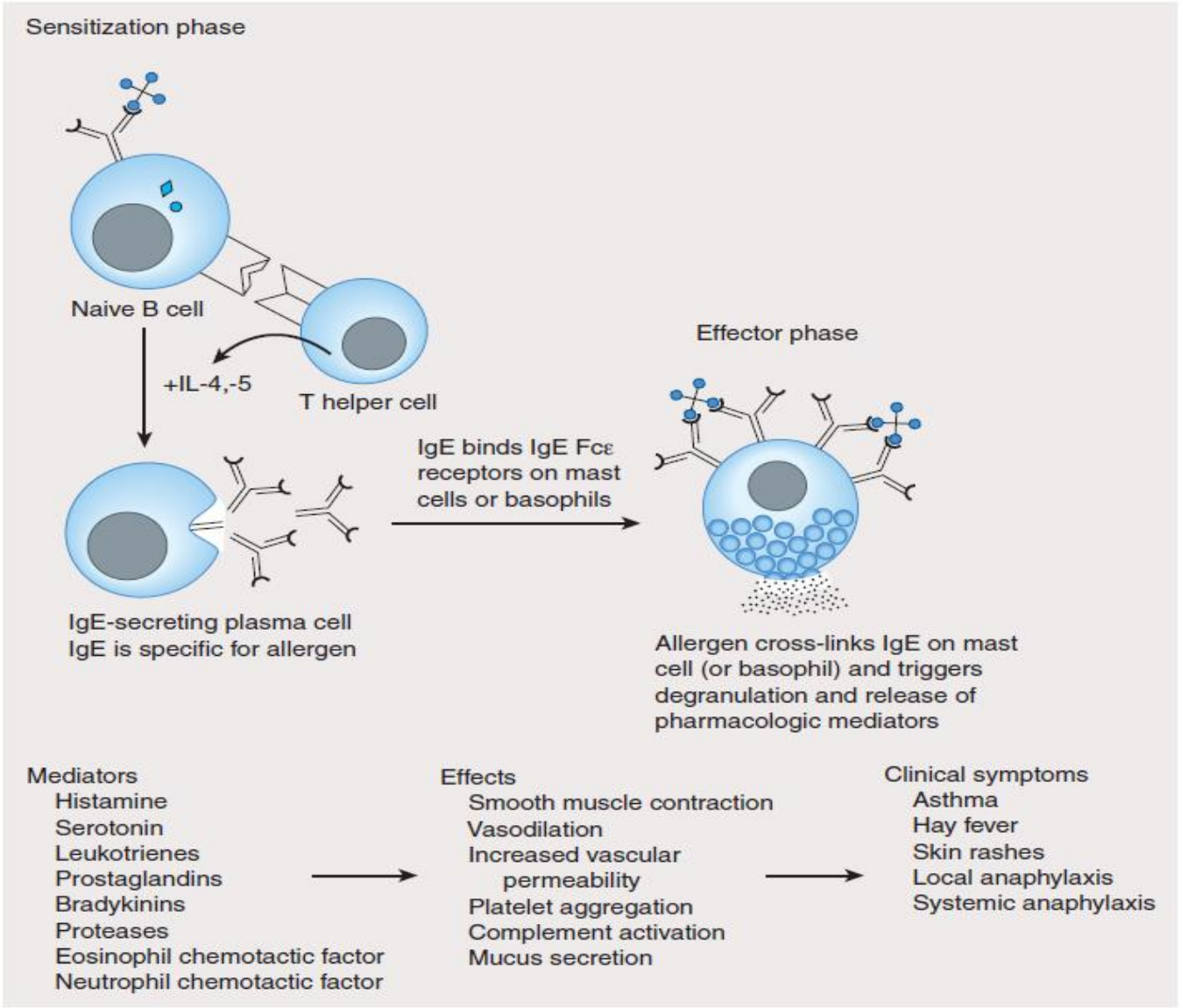

FIGURE 55–5 Mechanism of type I hypersensitivity. Initial exposure to allergen **(sensitization phase)** leads to production of IgE by plasma cells differentiated from allergen-specific B cells (not shown). The secreted IgE binds IgE-specific receptors (FcεR) on blood basophils and tissue mast cells. Reexposure to allergen leads to cross-linking of membrane-bound IgE **(effector phase).** This cross-linking causes degranulation of cytoplasmic granules and release of mediators that induce vasodilation, smooth muscle contraction, and increased vascular permeability. These effects lead to the clinical symptoms characteristic of type I hypersensitivity.

Histamine

Endogenous histamine modulates a variety of inflammatory and immune responses:

1. Local vasodilation and leakage of plasma-containing mediators of acute inflammation (complement, C-reactive protein) and antibodies.

2. Active chemotactic attraction for inflammatory cells (neutrophils, eosinophils, basophils, monocytes, and lymphocytes).

Histamine

3. **Inhibition of the release of lysosome contents and several T- and B-lymphocyte functions, mediated by H_2 or H_4 receptors.**
4. **Release of peptides from nerves in response to inflammation, probably modulated by histamine acting on presynaptic H_3-receptors.**

Histamine

2. Chemical and mechanical release:

- **Certain amines (morphine and tubocurarine) can displace histamine from binding sites within cells, which does not require energy and is not associated with mast cell injury or degranulation.**
- **Loss of granules from mast cells also release histamine through displacement by extracellular Na^+.**
- **Chemical and mechanical mast cell injury causes degranulation and histamine release.**

Histamine

Pharmacodynamics:

A. Mechanism of Action:

- **Histamine exerts its actions by combining with cell surface receptors, H_1, H_2, H_3, & H_4.**
- **All are coupled with G proteins.**
- **Activation of H_3 receptors decreases transmitter release from histaminergic and other neurons.**
- **H_4 receptors have chemotactic effects on eosinophils and mast cells.**

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 trisphosphate.

Histamine

B. Organ-system effects:

1. **Nervous system:**

- **Stimulation of sensory nerve endings especially those mediating pain and itching (H_1). This is an important component of the urticarial response and reaction to insect and nettle stings.**
- **Respiratory neurons signaling inspiration and expiration are modulated by H_1 receptors.**

Histamine

- **Presynaptic H_3 receptors activation modulate transmitter release (acetylcholine, amine and peptide NTs) in the peripheral and central nervous systems.**
- **An investigational inverse H_3 agonist, pitolisant, appears to reduce drowsiness in patients with *narcolepsy*.**

Histamine

- **H_1 and H_3 receptors play important roles in appetite and satiety. Antipsychotic drugs that block these receptors cause significant weight gain.**

Histamine

2. **Cardiovascular system:**

- **Vasodilation of arterioles and precapillary sphincters → reduction of blood pressure, flushing, sense of warmth and headache.**
- **Stimulation of the heart both directly (H_2) and by reflex mechanisms → tachycardia.**

Histamine

- **Small doses of histamine produce vasodilation through H_1 receptor activation which is mediated by nitric oxide release from the endothelium.**
- **High doses of histamine activate H_2 receptor and produce vasodilation by cAMP-mediated process.**

Histamine

- **Actions on postcapillary vessels (H_1) leads to separation of endothelial cells and transudation of fluid and electrolytes and small proteins into the perivascular tissues → edema. This effect is responsible for urticaria (hives), which signals the release of histamine in the skin.**
- **Some of the cardiovascular effects during anaphylaxis may be due to other factors.**

Histamine

3. **Bronchial smooth muscle:**

- **Bronchoconstriction (H_1) especially in patients with bronchial asthma (100-1000 times more sensitive to histamine).**

4. **Gastrointestinal smooth muscles:**

- **Large doses of histamine contract GIT smooth muscle and may induce diarrhea (H_1).**

5. **Pregnant women suffering from anaphylactic reactions may abort as a result of histamine-induced uterine contractions**

Histamine

6. Secretory tissue:

- **Powerful stimulation of gastric acid secretion (H_2), and to a lesser extent, of gastric pepsin and intrinsic factor production.**
- **Histamine also stimulates secretion in the small and large intestine.**
- **H_3 receptor activation inhibit gastric acid secretion.**

Histamine

7. Metabolic effects:

- **Absence of H_3-receptor results in increased food intake, decreased energy expenditure, and obesity, in addition to insulin resistance and increased blood levels of leptin and insulin.**
- **The clinical significance of this (especially in treatment of obesity) is yet to be determined.**

Histamine

8. The “triple response”:

- At the site of injection, a reddening appears owing to dilation of small vessels, followed soon by an edematous wheal at the injection site and a red irregular flare surrounding the wheal. The flare is said to be caused by an axon reflex.

Histamine

- **A sensation of itching may accompany these effects.**
- **The effect involves 3 separate cell types: smooth muscle in the microcirculation, capillary or venular endothelium, and sensory nerve endings.**
- **These effects mainly involve H_1 receptor activation. H_2 and H_3 receptors may also be involved.**

Histamine

Clinical pharmacology:

- **No significant clinical application except its use as an aerosol as a provocative test of bronchial hyperreactivity (for diagnostic purposes).**

Adverse effects:

- **Flushing, hypotension, tachycardia, headache, wheals, bronchoconstriction and GIT upset.**
- **These effects are observed after ingestion of spoiled fish. Histamine is produced by bacteria acting on the flesh of fish.**

Histamine Antagonists

1. **Physiologic antagonists: Epinephrine acting on different receptors (adrenergic receptors) produces actions opposite to those of histamine. It is life-saving in systemic anaphylaxis.**
2. **Release inhibitors: Cromolyn, and β_2-adrenoceptor agonists.**

Histamine Antagonists

3. **Receptor antagonists:**

- **H_1-receptor antagonists.**
- **H_2-receptor antagonists.**
- **Potent and partially selective experimental H_3-receptor antagonists, thioperamide and clobenpropit, have been developed.**

H_1-Receptor Antagonists

- They competitively and reversibly block histamine at H_1 receptor, or act as inverse agonists at H_1 receptors.

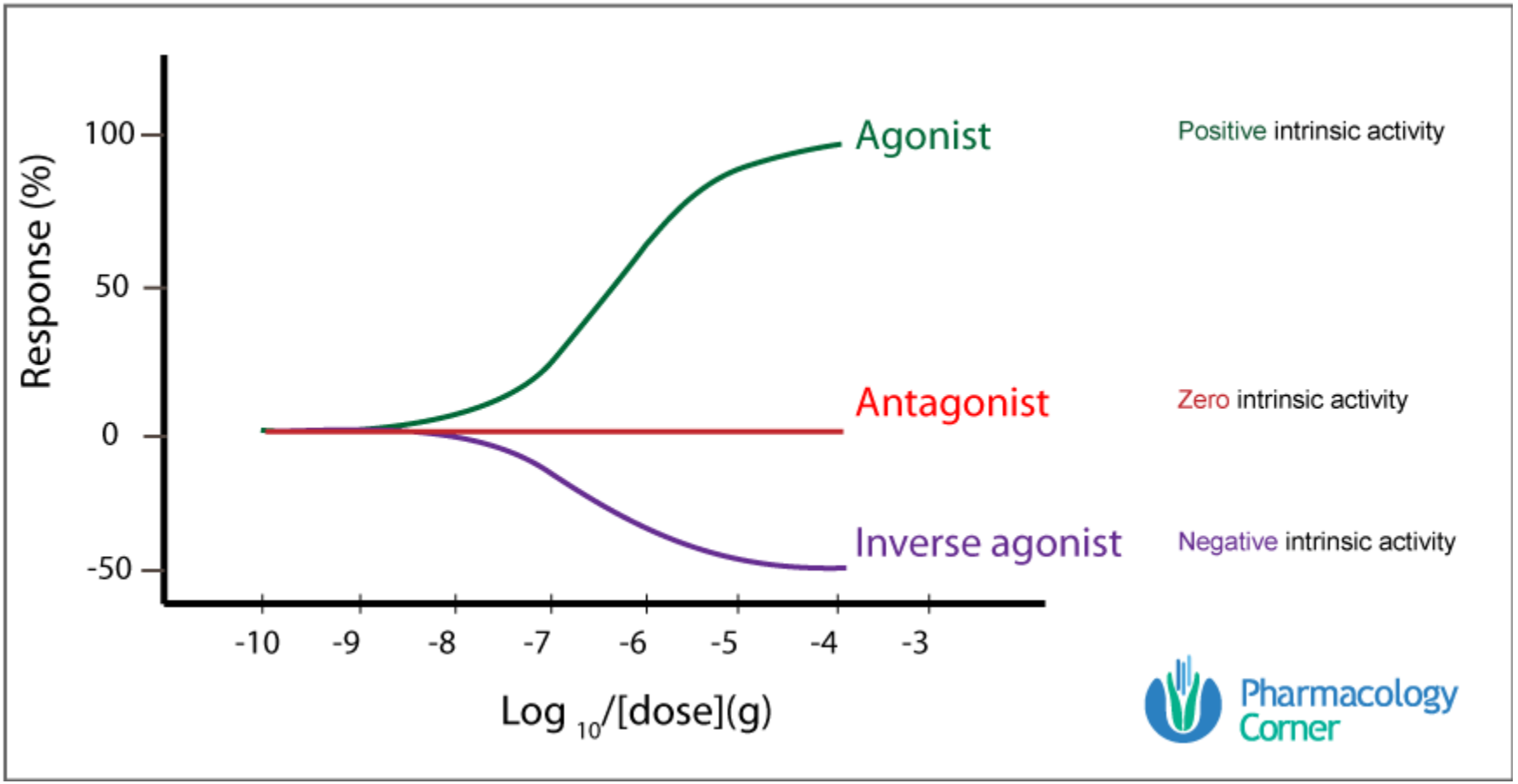
Response (%)
100
50
0
-50
-10
-9
-8
-7
-6
-5
-4
-3
Log 10/[dose](g)
Agonist
Antagonist
Inverse agonist
Positive intrinsic activity
Zero intrinsic activity
Negative intrinsic activity
Pharmacology Corner

TABLE 16–2 Some H_1 antihistaminic drugs in clinical use.

Drugs	Usual Adult Dose	Anticholinergic 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
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 derivative			
Promethazine (Phenergan, etc)	10–25 mg	+++	Marked sedation; antiemetic; α block
Miscellaneous			
Cyproheptadine (Periactin, etc)	4 mg	+	Moderate sedation; significant antiserotonin activity
SECOND-GENERATION ANTIHISTAMINES			
Piperidine			
Fexofenadine (Allegra)	60 mg	–	
Miscellaneous			
Loratadine (Claritin), desloratadine (Clarinex)	10 mg (desloratadine, 5 mg)	–	Longer action; used at 5 mg dosage
Cetirizine (Zyrtec)	5–10 mg	–	

nd, no data found.

H_1-Receptor Antagonists

Pharmacokinetics:

- **Rapidly absorbed following oral administration.**
- **Widely distributed throughout the body and first-generation agents also enter the CNS.**
- **Eliminated primarily by metabolism in the liver by microsomal enzymes (P450s or CYPs).**
- **Second-generation agents are primarily metabolized by CYP3A4 system and are subject to tremendous drug-drug interactions.**

H_1-Receptor Antagonists

- **Meclizine and second generation agents are long-acting (1-2 times daily vs 4 times daily).**
- **The newer agents are less lipid soluble and are substrates for the P-glycoprotein transporter in the blood-brain barrier, and thus are excluded from the CNS**
- **Many have active metabolites that are also drugs (hydroxyzine, terfenadine, loratadine → cetirizine, fexofenadine, desloratadine).**

H_1-Receptor Antagonists

Pharmacodynamics:

A. Actions caused by histamine-receptor blockade:

- **Both neutral H_1 antagonists and inverse H_1 agonists reduce or block the actions of histamine by reversible competitive binding to the H_1 receptor.**
- **They have negligible potency at the H_2 receptor and little at the H_3 receptor.**

H_1-Receptor Antagonists

B. Actions NOT caused by histamine-receptor blockade:

- **Due to similarity in chemical structure to drugs acting on muscarinic receptors, α-adrenoceptors, serotonin and local anesthetic receptor sites.**
- **Some of these actions are of therapeutic value and some are undesirable.**

H_1-Receptor Antagonists

1. **Sedation:**

- **This effect is common with first-generation H_1 antagonists, making them useful as ‘sleep aids” and unsuitable for daytime use.**
- **Children occasionally (and adults rarely) manifest excitation rather than sedation, at ordinary doses.**
- **Toxic drug levels produce stimulation, agitation, seizures and coma.**

H_1-Receptor Antagonists

- **Second-generation H_1 antagonists have little or no sedative or stimulant actions, and fewer autonomic effects than the first-generation antihistamines.**

2. **Antinausea and antiemetic actions and prevention of motion sickness.**
3. **Anticholinergic actions or atropine-like effects on peripheral muscarinic receptors.**

H_1-Receptor Antagonists

4. **Antiparkinsonism effects: diphenhydramine is given parenterally for acute dystonic reactions to antipsychotics.**
5. **α-Adrenoceptor blocking effects. Promethazine may cause orthostatic hypotension.**
6. **Serotonin-blocking actions by first generation agents particularly cyproheptadine.**

H_1-Receptor Antagonists

7. **Local anesthesia: Several first generation agents block Na^+ channels in excitable membranes. Diphenhydramine and promethazine.**
8. **Cetirizine blocks mast cell release of histamine which is not due to H_1 blockade and may reflect an H_4-receptor effect.**

H_1-Receptor Antagonists

Clinical Uses:

1. **Allergic reactions:**

- **Treatment and prevention of allergic reactions, allergic rhinitis and urticarial.**
- **Not useful in bronchial asthma.**

2. **Motion sickness and vestibular disturbances: first-generation agents.**
3. **Nausea and vomiting of pregnancy: Doxylamine + pyridoxine = Bendectin**

- **Be ware of teratogenicity.**

H_1-Receptor Antagonists

Adverse effects and toxicity:

1. **Sedation: first generation**
2. **Antimuscarinic effects: blurring of vision, dryness of secretions, urine retention, ..**
3. **Excitation and convulsions in children.**
4. **Postural hypotension.**
5. **Allergic reactions (after topical use).**
6. **Cardiac arrhythmias: astemizole, terfenadine were withdrawn because of this side effects.**

H_1-Receptor Antagonists

Drug Interactions:

1. **Fatal polymorphic ventricular arrhythmias occurred in several patients taking combination of second generation agents with ketoconazole, macrolide antibiotics and other drugs metabolized by CYP3A4 because of competition for metabolism. Accumulation of the second generation agents in the blood blocks cardiac potassium channels (I_{Kr}) that contribute to repolarization. The result is action potential prolongation, QT- prolongation.**

H_1-Receptor Antagonists

2. **Grapefruit juice also inhibits CYP3A4 and leads to accumulation of second generation agents**
3. **First generation agents increase the action of sedative-hypnotic drugs.**
4. **First generation agents increase the action of antimuscarinic and α-adrenoceptor blockers.**

Serotonin (5-Hydroxytryptamine)

- A metabolite of 5-hydroxytryptophan.
- Is a neurotransmitter.
- Is a local hormone in the gut.
- Is a component of the platelet clotting process.
- Is thought to play a role in migraine headache
- Is secreted (+ others) by carcinoid tumor, a neoplasm of enterochromaffin cells.

Serotonin

Pharmacokinetics:

- **Widely distributed in nature: plants, animal tissue, venoms and stings.**
- **Formed from L-tryptophan by hydroxylation followed by decarboxylation.**
- **After synthesis, the free amine is either stored or rapidly inactivated by monoamine oxidase (MAO) to 5-hydroxyindolacetic acid (a diagnostic test for carcinoid tumor).**

Serotonin

- **It is a precursor of melatonin (pineal gland).**
- **In the body, over 90% of serotonin is found in the enterochromaffin cells of the GIT.**
- **Platelets concentrate serotonin by the active serotonin transporter (SERT) similar to that present in serotonergic nerve endings.**
- **Once transported it is concentrated in vesicles by the vesicle-associated transporter (VAT) that is blocked by reserpine.**

Serotonin

- **Serotonin is also found in the raphe nuclei of the brainstem, which contain cell bodies of serotonergic neurons that synthesize, store, and release serotonin as a transmitter.**
- **Stored serotonin can be depleted by reserpine.**
- **It is also found in mast cells.**
- **Bananas are rich in serotonin or its precursors.**

Serotonin

- **Brain serotonergic neurons are involved in numerous diffuse functions such as: mood, sleep, appetite, temperature regulation, perception of pain, vomiting, and regulation of blood pressure.**
- **Seems to be involved in clinical conditions such as depression, anxiety and migraine.**
- **Serotonergic neurons are also found in the enteric nervous system of the GIT and around blood vessels.**

Serotonin

Pharmacodynamics:

A. Mechanism of action:

- **Actions are mediated through a large number of cell membrane receptors, 7 families of receptors (5-HT_{1-7}) with various subtypes. Six of them are G-protein coupled, and one (5-HT_3) a ligand-gated ion channel.**

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	LY3344864[1]	
5-HT_{1P}	Enteric nervous system	G_o, 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 trisphosphate.

Serotonin

B. Tissue and organ system effects:

1. **Nervous system:**

- **Acts as a neurotransmitter in a variety of sites in the brain. (CNS pharmacology)**
- **Is a precursor of melatonin in the pineal gland. (is involved in the sleep-wake behavior, and may be useful as sleep aid).**

Serotonin

- **Repinotan, a 5-HT_{1A} agonist currently in clinical trials, have some antinociceptive action at higher doses while reversing opioid-induced respiratory depression.**

Serotonin

- **5-HT_3 receptors in the GIT and in the vomiting center are involved in the vomiting reflex. They are particularly involved in vomiting induced by chemical triggers such as cancer chemotherapy.**
- ***It is a potent stimulant of pain and itch sensory nerve endings responsible for the symptoms produced by insect and plant stings.***

Serotonin

- **It activates 5-HT_3 receptors in vagal afferents (chemosensitive endings) in the coronary vascular bed → chemoreceptor reflex manifested by bradycardia and hypotension.**
- **The bradycardia is mediated by vagal outflow to the heart and can be blocked by atropine.**
- **The hypotension is a consequence of the decrease in cardiac output that results from bradycardia.**

Serotonin

2. **Respiratory system:**

- **Mild bronchoconstriction (5-HT_{2A} receptors).**
- **Facilitates acetylcholine release from bronchial vagal nerve endings.**
- **Hyperventilation as a result of a chemoreceptor reflex or stimulation of bronchial sensory nerve endings.**

Serotonin

3. **Cardiovascular system:**

- **Contraction of vascular smooth muscle, mainly through 5-HT_2 receptors, except in skeletal muscles and heart where it dilates blood vessels. Vasodilation requires intact endothelium.**
- **Reflex bradycardia through activation of 5-HT_3 receptors on chemoreceptor nerve endings.**

Serotonin

- Venoconstriction → increased capillary filling → flushing.
- Prolonged elevation of blood serotonin (carcinoid syndrome) is associated with subendocardial fibroplasia → valvular or electrical malfunction.
- Platelet aggregation by activating surface 5-HT_2 receptors.

Serotonin

4. **Gastrointestinal tract:**

- **Stimulation of GI smooth muscle, increasing tone and facilitating peristalsis (5-HT_2 smooth muscle receptors and stimulation of ganglion cells in the enteric nervous system). 5-HT_{1A} and 5-HT_7 receptors may also be involved.**

Serotonin

- **Motility-enhancing or prokinetic effect due to an increase of acetylcholine release by activation of 5-HT_4 receptors in enteric nervous system.**
- **Overproduction of serotonin (and other substances) in carcinoid tumor is associated with severe diarrhea.**

Serotonin Syndrome

- **Potentially fatal syndrome, due to excess synaptic serotonin, or drugs that increase brain content of serotonin.**
- **It is predictable and not idiosyncratic.**
- **Precipitating drugs:**

1. **Serotonin selective reuptake inhibitors (SSRIs).**
2. **Second generation antidepressants.**
3. **Monoamine oxidase inhibitors (MAOIs).**

Serotonin Syndrome

4. **Many others, and combinations of the above.**

- **Manifested within hours by hypertension, hyperreflexia, tremor, clonus, hyperthermia, hyperactive bowel sounds, diarrhea, mydriasis, agitation, coma.**

TABLE 16–4 Characteristics of serotonin syndrome and other hyperthermic syndromes.

Syndrome	Precipitating Drugs	Clinical Presentation	Therapy[1]
Serotonin syndrome	SSRIs, second-generation antidepressants, MAOIs, linezolid, tramadol, meperidine, fentanyl, ondansetron, sumatriptan, MDMA, LSD, St. John's wort, ginseng	Hypertension, hyperreflexia, tremor, clonus, hyperthermia, hyperactive bowel sounds, diarrhea, mydriasis, agitation, coma; onset within hours	**Sedation (benzodiazepines), paralysis, intubation, and ventilation;** consider 5-HT_2 block with cyproheptadine or chlorpromazine
Neuroleptic malignant syndrome	D_2-blocking antipsychotics	Acute severe parkinsonism; hypertension, hyperthermia, normal or reduced bowel sounds, onset over 1–3 days	**Diphenhydramine** (parenteral), cooling if temperature is very high, sedation with benzodiazepines
Malignant hyperthermia	Volatile anesthetics, succinylcholine	Hyperthermia, muscle rigidity, hypertension, tachycardia; onset within minutes	**Dantrolene,** cooling

[1]Precipitating drugs should be discontinued immediately. First-line therapy is in **bold** font.

MAOIs, monoamine oxidase inhibitors; MDMA, methylenedioxy-methamphetamine (ecstasy); SSRIs, selective serotonin reuptake inhibitors.

Serotonin & Its Agonists

Clinical Pharmacology:

- **Serotonin has no clinical applications as a drug.**
- **Some agonists are of value:**

1. **Buspirone (5-HT_{1A}): Anxiolytic.**
2. **Dexfenfluramine (5-HT_{2C}): Appetite suppression – very toxic. → cardiac valvulopathy.**
3. **Lorcaserin, 5-HT2C agonist, has recently been approved by the FDA for use as a weight-loss medication.**

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4. **Sumatriptan** (5-HT_{1D} and 5-HT_{1B}): **Acute migraine and cluster headache** (vascular headaches). → vasoconstriction in cerebral and meningeal vessels. Activation of 5-HT1D/1B receptors on presynaptic trigeminal nerve endings may inhibit the release of vasodilating peptides
5. **Tegaserod** (5-HT_4): **Irritable bowel syndrome with constipation**.
6. SSRIs (**fluoxetine**): **Depression**.

Serotonin-Receptor Antagonists

Useful in carcinoid tumor and other conditions.

Cyproheptadine:

- **Resembles phenothiazene antihistamines.**
- **Blocks histamine H_1 receptors.**
- **Blocks 5-HT_2 receptors.**
- **Blocks the smooth muscle effects of both amines, but does not block histamine induced gastric acid secretion.**
- **Has significant antimuscarinic effect, and causes sedation.**

Serotonin-Receptor Antagonists

Major clinical applications:

1. **Treatment of the smooth muscle manifestations of carcinoid tumor.**
2. **Cold-induced urticaria.**
3. **May be useful in serotonin syndrome.**
4. **May reduce muscle spasms following spinal cord injury, in which activity of 5-HT_{2C} receptors is associated with increases in Ca^{2+} currents leading to spasms.**

Serotonin-Receptor Antagonists

Ketanserin:

- **Blocks 5-HT_2 receptors on smooth muscle.**
- **Blocks vascular α_1- adrenoceptors (hypotension).**
- **Antagonizes platelet aggregation induced by serotonin (5-HT_2).**
- **Useful for hypertension and vaso-spastic conditions.**

Serotonin-Receptor Antagonists

Ritanserin:

- **Blocks 5-HT_2 receptors with no α_1-adrenoceptor blocking action.**
- **Reduces thromboxane formation by platelets.**

Ondansetron:

- **Blocks 5-HT_3 receptors.**
- **Used for prevention of nausea and vomiting associated with surgery and cancer chemotherapy.**

Melatonin

- **It is *N*-acetyl-5-methoxytryptamine, a product of serotonin found in the pineal gland.**
- **It is produced and released primarily at night and suspected of playing a role in the sleep-wake behavior of humans.**
- **Melatonin receptors in the brain, MT_1 and MT_2, are found in membranes of neurons in the suprachiasmatic nucleus of the hypothalamus, an area associated with circadian rhythm.**

Melatonin

- **MT_1 and MT_2 are Gi protein-coupled receptors. The result of receptor binding is inhibition of adenylyl cyclase.**
- **A third receptor, MT_3, is an enzyme; with a poorly defined physiologic role, possibly related to intraocular pressure.**

Melatonin

- **Activation of the MT_1 receptor results in sleepiness, whereas the MT_2 receptor may be related to synchronization of the biologic circadian clock.**

Melatonin may also have the following actions:

- **Anti-apoptotic effects.**
- **May be involved in depressive disorders.**
- **It may ameliorate jet lag.**

Melatonin Agonists

- **Ramelteon** is a selective MT_1 and MT_2 agonist – treatment of **insomnia**.
- **Tasimelteon** is a newer MT_1 and MT_2 agonist – used for the **"non-24-hour sleep-wake disorder"** (circadian rhythm disorder).
- **Agomelatine** is an MT_1 and MT_2 agonist and a 5-HT_{2C} antagonist – used in major **depression**.