AUTOCOIDS

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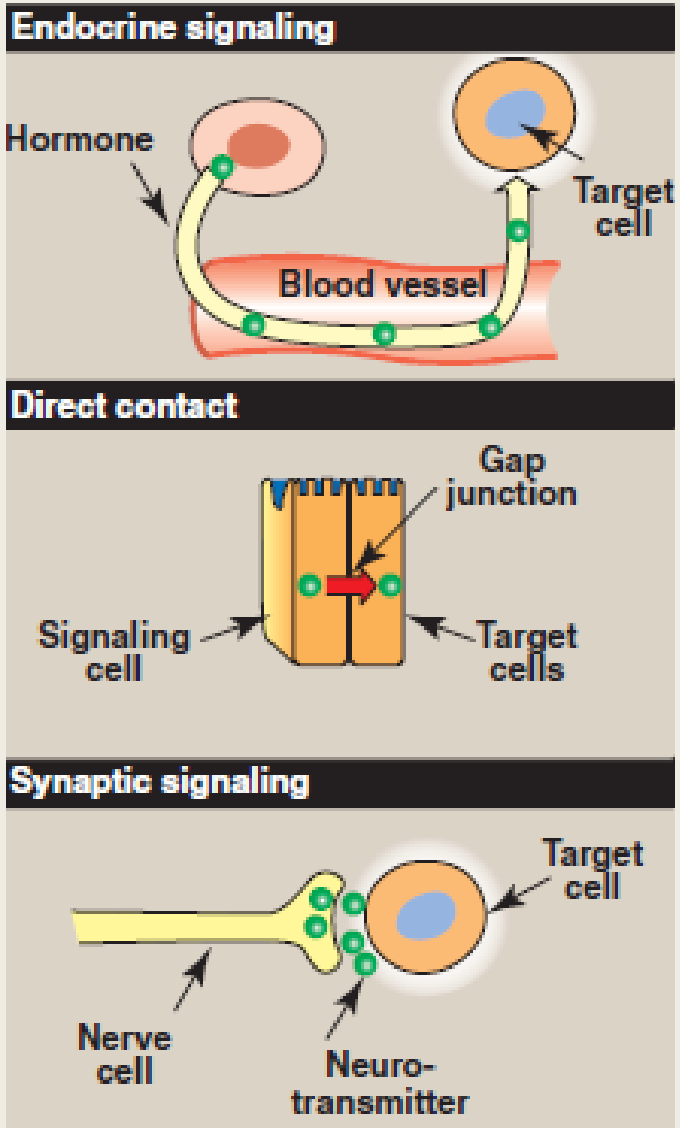
Figures and tables are originated from Lippincott's Pharmacology (6th Edition) and Katzung&Trevor Basic and Clinical Pharmacology (13th Edition).



Specialized endocrine cells secrete hormones into the bloodstream,where they travel throughout the body, exerting effects on broadly distributed target cells.

Most cells in the body secrete chemicals that act locally on cells in the immediate environment. Because these chemical signals are rapidly destroyed or removed, they do not enter the blood and are not distributed throughout the body.

Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals (neurotransmitters) from the nerve terminals. This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization.

Histamine

Histamine is a chemical messenger mostly generated in mast cells. Histamine, via multiple receptor systems, mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain. Histamine has no clinical applications, but agents that inhibit the action of histamine (antihistamines or histamine receptor blockers) have important therapeutic applications.

H_1 ANTIHISTAMINES

Alcaftadine LASTACAFT
Azelastine ASTELIN, OPTIVAR
Bepotastine BEPREVE
Brompheniramine LO-HIST, VAZOL
Cetirizine ZYRTEC
Chlorpheniramine CHLOR-TRIMETON
Clemastine TAVIST ALLERGY
Cyclizine MAREZINE
Cyproheptadine
Desloratadine CLARINEX
Diphenhydramine BENADRYL
Dimenhydrinate DRAMAMINE
Doxylamine UNISOM SLEEPTABS
Emedastine EMADINE
Fexofenadine ALLEGRA
Hydroxyzine VISTARIL, ATARAX
Ketotifen ALAWAY, ZADITOR
Levocetirizine XYZAL
Loratadine CLARITIN
Meclizine BONINE, ANTIVERT
Olopatadine PATANASE, PATANOL
Promethazine PHENERGAN

H_2 – HISTAMINE RECEPTOR BLOCKERS

Cimetidine TAGAMET
Famotidine PEPCID
Nizatidine AXID
Ranitidine ZANTAC

Location, synthesis, and release of histamine

1. **Location:** Histamine is present in practically all tissues, with significant amounts in the lungs, skin, blood vessels, and GI tract. It is found at high concentration in mast cells and basophils. Histamine functions as a neurotransmitter in the brain.
2. **Synthesis:** Histamine is an amine formed by the decarboxylation of the amino acid histidine by the enzyme histidine decarboxylase, which is expressed in cells throughout the body, including neurons, gastric parietal cells, mast cells, and basophils. In mast cells, histamine is stored in granules.
3. **Release of histamine:** Most often, histamine is just one of several chemical mediators released in response to stimuli. The stimuli for release of histamine from tissues may include destruction of cells as a result of cold, toxins from organisms, venoms from insects and spiders, and trauma. Allergies and anaphylaxis can also trigger significant release of histamine.

Role in allergy and anaphylaxis

The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions. These include contraction of airway smooth muscle, stimulation of secretions, dilation and increased permeability of the capillaries, and stimulation of sensory nerve endings.

Histamine released in response to certain stimuli exerts its effects by binding to various types of histamine receptors (H1, H2, H3, and H4). H1 and H2 receptors are widely expressed and are the targets of clinically useful drugs. The H1 receptors are important in producing smooth muscle contraction and increasing capillary permeability. Histamine promotes vasodilation of small blood vessels by causing the vascular endothelium to release nitric oxide. In addition, histamine can enhance the secretion of proinflammatory cytokines in several cell types and in local tissues. Histamine H1 receptors mediate many pathological processes, including allergic rhinitis, atopic dermatitis, conjunctivitis, urticaria, bronchoconstriction, asthma, and anaphylaxis. Moreover, histamine stimulates the parietal cells in the stomach, causing an increase in acid secretion via the activation of H2 receptors.

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] proxyfan
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.

H_1 Receptors

EXOCRINE EXCRETION

Increased production of nasal and bronchial mucus, resulting in respiratory symptoms.

BRONCHIAL SMOOTH MUSCLE

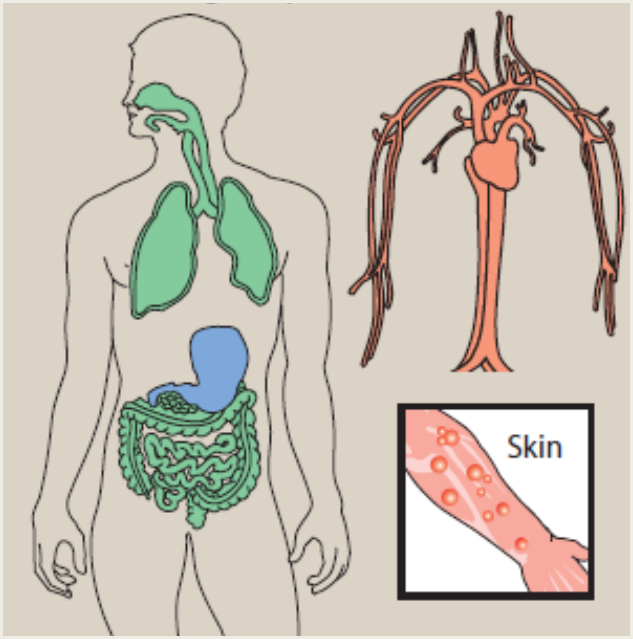
Constriction of bronchioles results in symptoms of asthma and decreased lung capacity.

INTESTINAL SMOOTH MUSCLE

Constriction results in intestinal cramps and diarrhea.

SENSORY NERVE ENDINGS

Causes itching and pain.



H_1 and H_2 Receptors

CARDIOVASCULAR SYSTEM

Lowers systemic blood pressure by reducing peripheral resistance. Causes positive chronotropism (mediated by H_2 receptors) and a positive inotropism (mediated by both H_1 and H_2 receptors).

SKIN

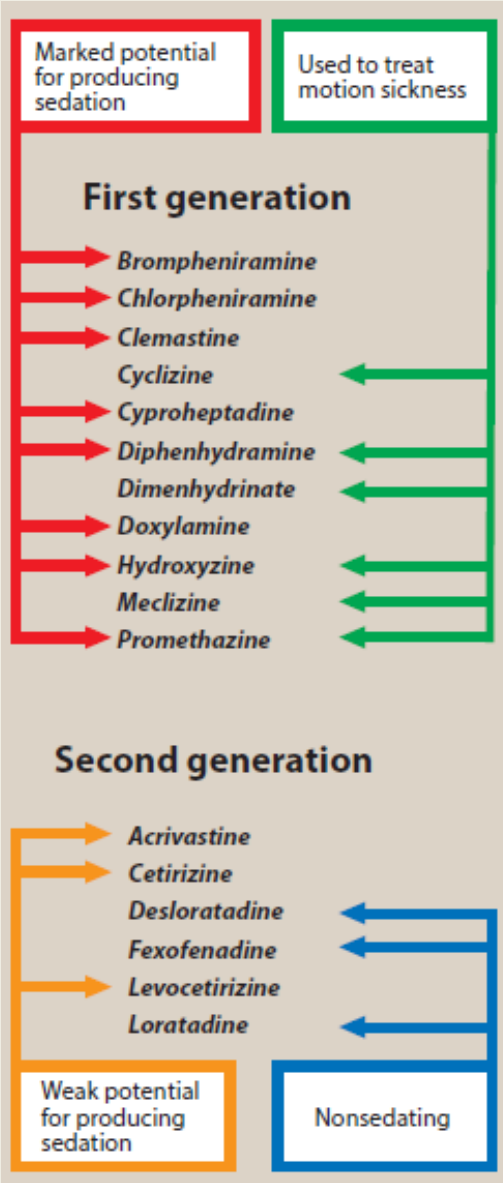
Dilation and increased permeability of the capillaries results in leakage of proteins and fluid into the tissues. In the skin, this results in the classic "triple response": wheal formation, reddening due to local vasodilation, and flare ("halo").

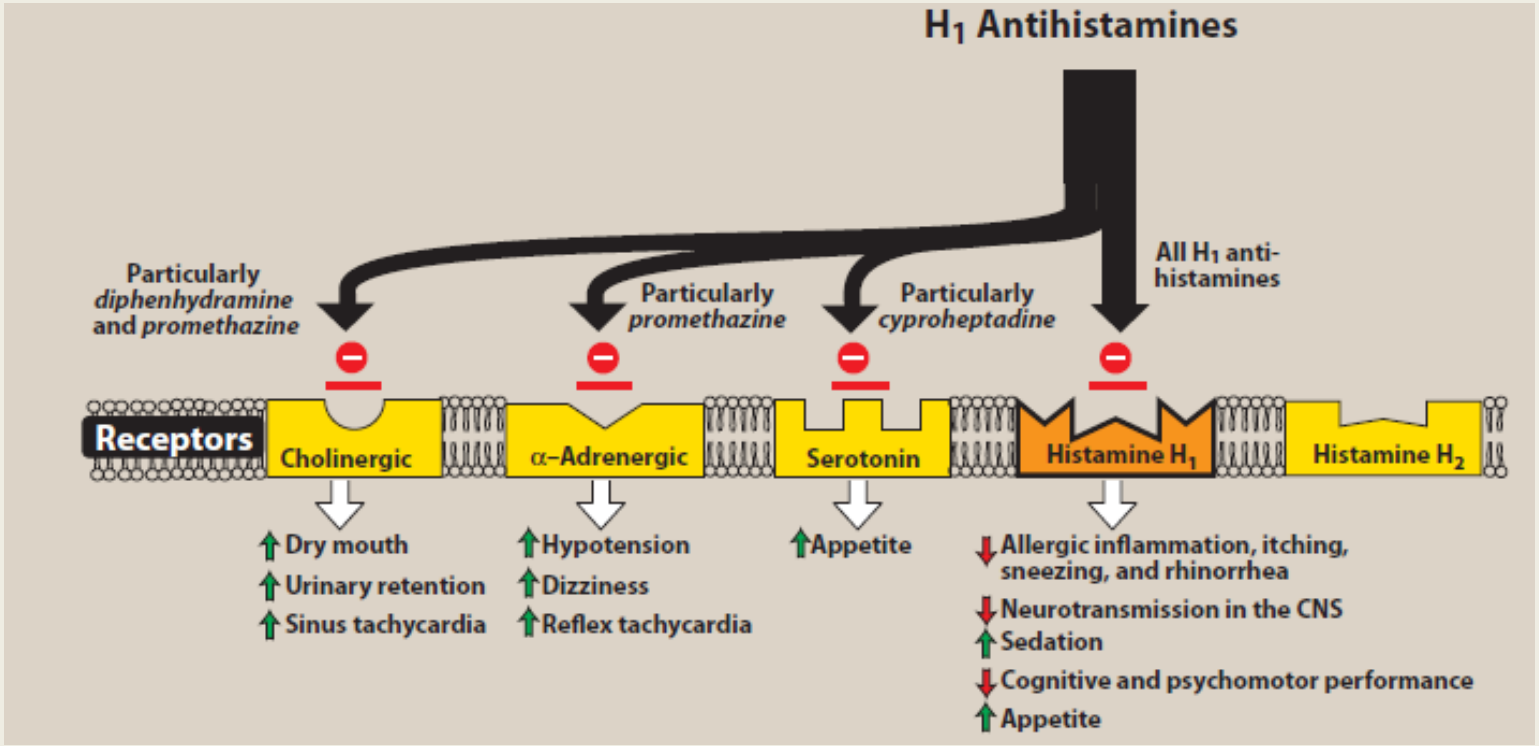
H_2 Receptors

STOMACH

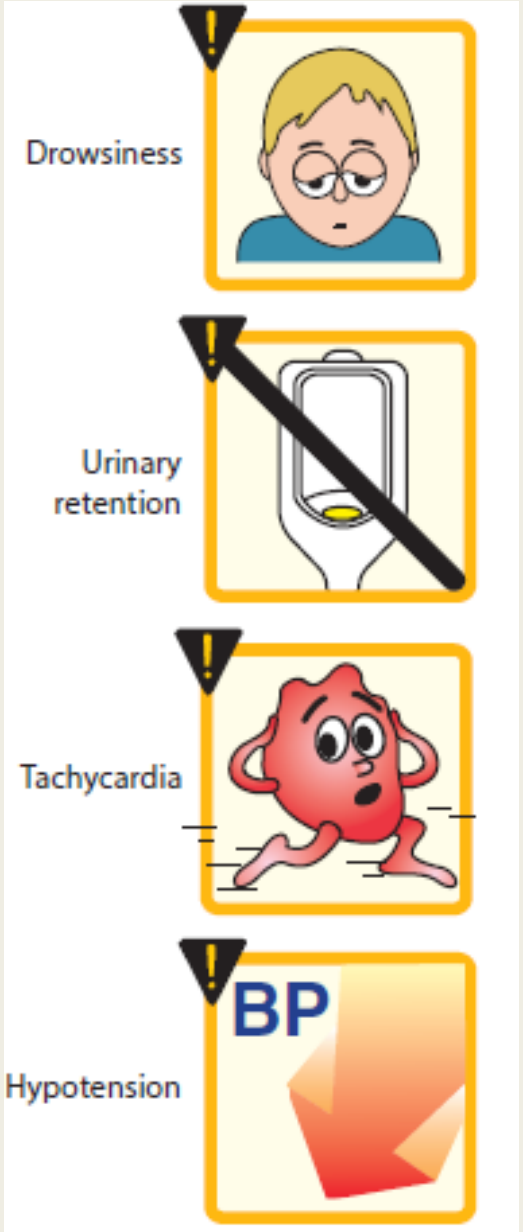
Stimulation of gastric hydrochloric acid secretion.

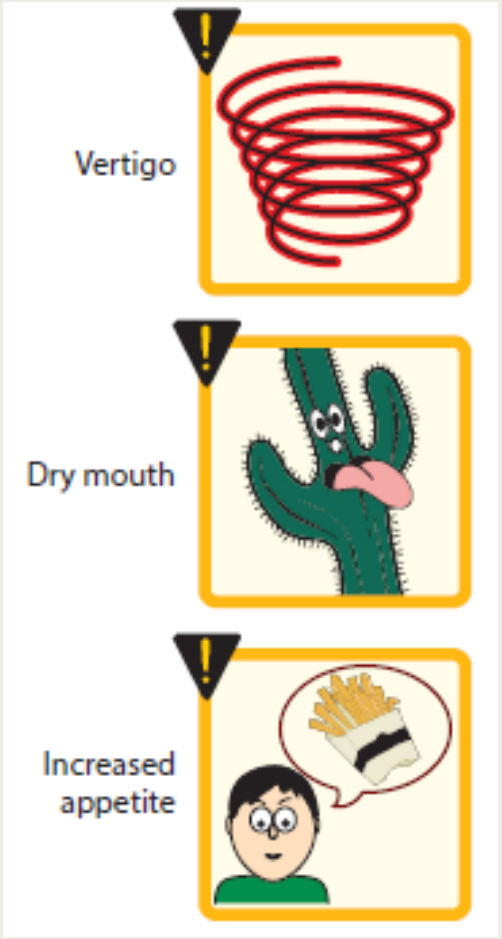
H_1 Antihistamines





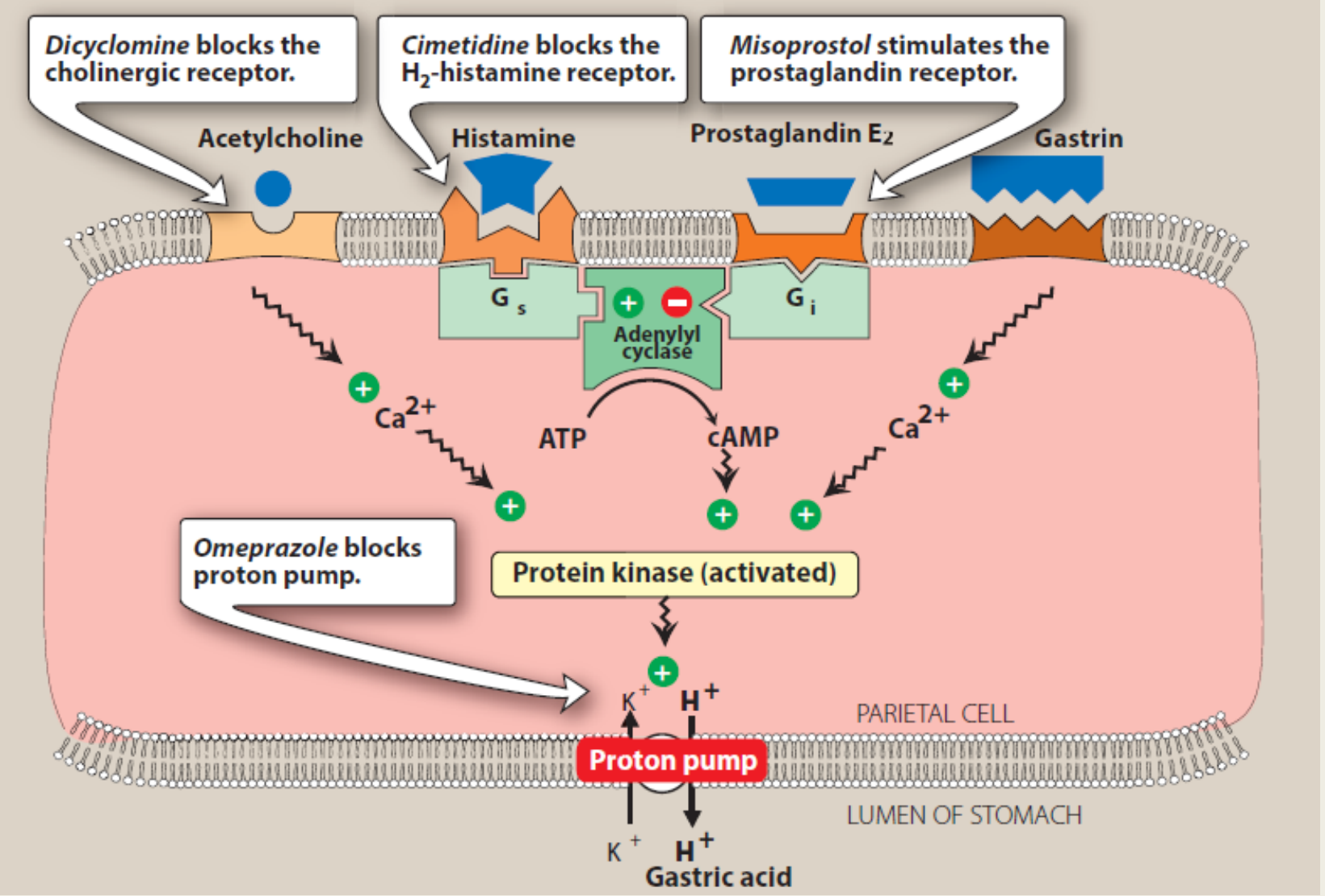
Allergic and inflammatory conditions
Motion sickness and nausea
Somnifacients


Drowsiness
Urinary retention
Tachycardia
BP
Hypotension


Vertigo
Dry mouth
Increased appetite

H2 Antihistamines

Gastric acid secretion is stimulated by acetylcholine, histamine, and gastrin.



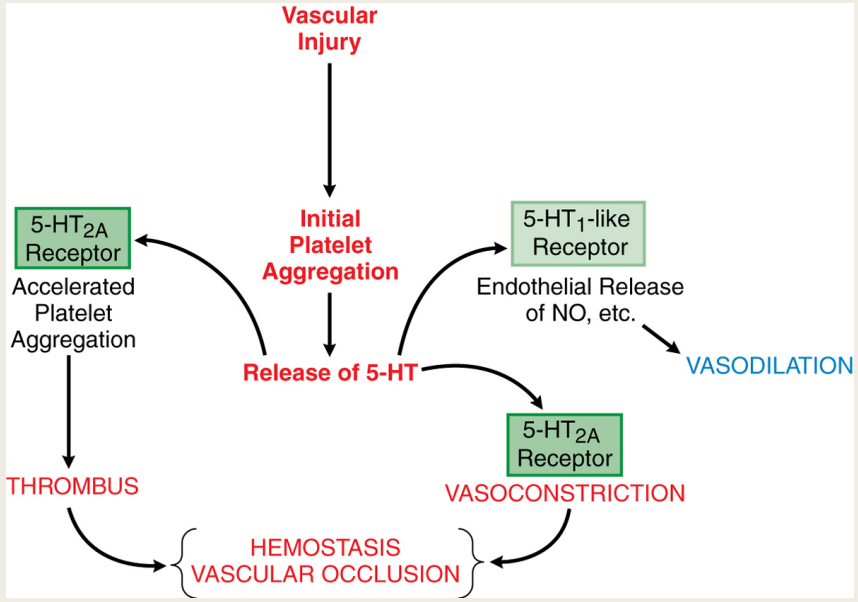
Serotonin

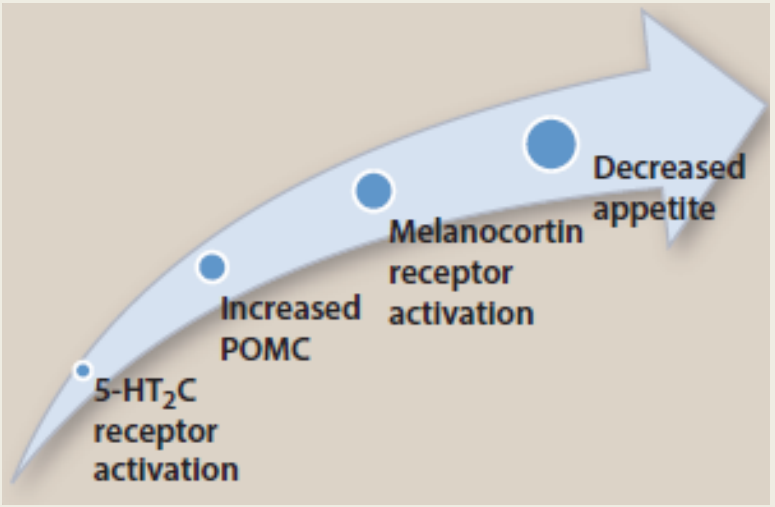
Serotonin is an important neurotransmitter, a local hormone in the gut, a component of the platelet clotting process, and is thought to play a role in migraine headache and several other clinical conditions, including carcinoid syndrome.

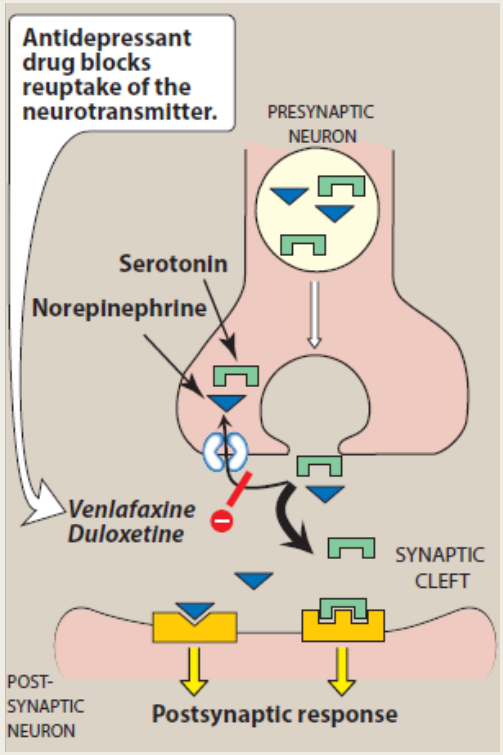
It is synthesized in biologic systems from the amino acid l-tryptophan. After synthesis, the free amine is stored in vesicles or is rapidly inactivated, usually by oxidation by monoamine oxidase (MAO).
In the pineal gland, serotonin serves as a precursor of melatonin.
In mammals (including humans), over 90% of the serotonin in the body is found in enterochromaffin cells in the gastrointestinal tract.
In the blood, serotonin is found in platelets.
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.

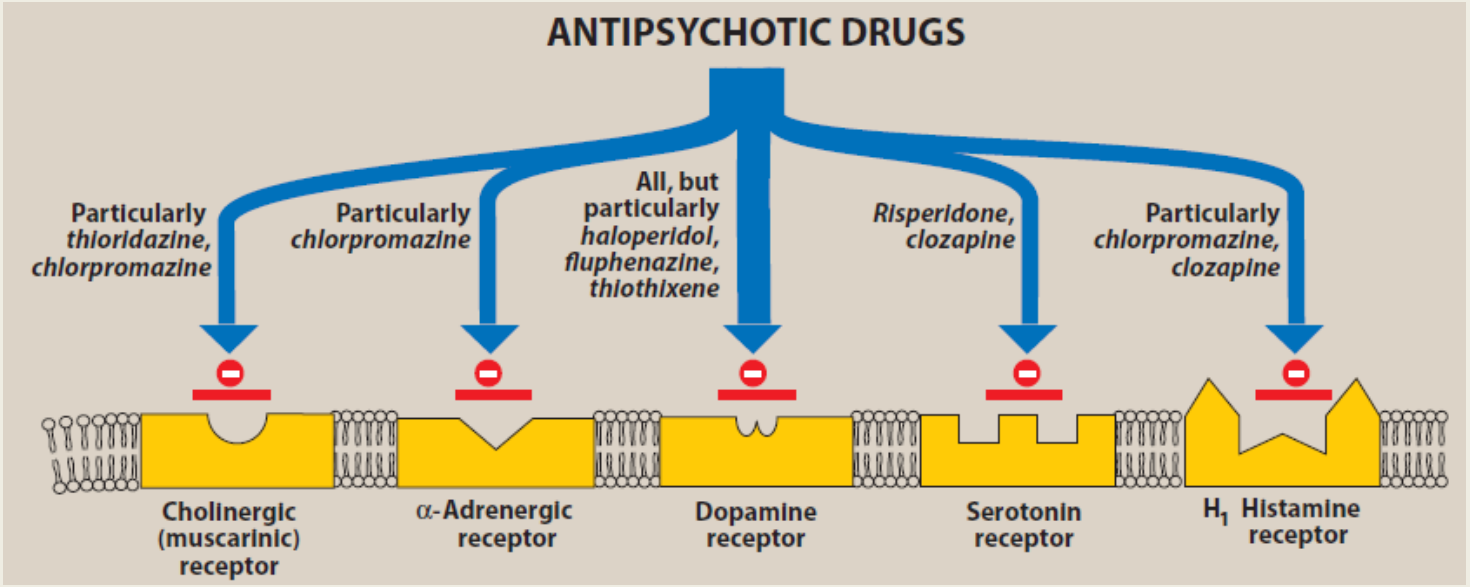
Brain serotonergic neurons are involved in numerous diffuse functions such as mood, sleep, appetite, and temperature regulation, as well as the perception of pain, the regulation of blood pressure, and vomiting. Serotonin is clearly involved in psychiatric depression and also appears to be involved in conditions such as anxiety and migraine.

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)


Vascular Injury
Initial Platelet Aggregation
5-HT2A Receptor
Accelerated Platelet Aggregation
5-HT1-like Receptor
Endothelial Release of NO, etc.
VASODILATION
Release of 5-HT
5-HT2A Receptor
VASOCONSTRICTION
THROMBUS
HEMOSTASIS
VASCULAR OCCLUSION


Decreased appetite
Melanocortin receptor activation
Increased POMC
5-HT2C receptor activation


Antidepressant drug blocks reuptake of the neurotransmitter.
PRESYNAPTIC NEURON
Serotonin
Norepinephrine
Venlafaxine
Duloxetine
SYNAPTIC CLEFT
POST-SYNAPTIC NEURON
Postsynaptic response


ANTIPSYCHOTIC DRUGS
Particularly thioridazine, chlorpromazine
Particularly chlorpromazine
All, but particularly haloperidol, fluphenazine, thiothixene
Risperidone, clozapine
Particularly chlorpromazine, clozapine
Cholinergic (muscarinic) receptor
α-Adrenergic receptor
Dopamine receptor
Serotonin receptor
H1 Histamine receptor

5-HT Receptor Agonists and Antagonists

Serotonergic Drugs: Primary Actions and Clinical Indications

RECEPTOR	ACTION	DRUG EXAMPLES	CLINICAL DISORDER
5-HT_{1A}	Partial agonist	Buspirone, ipsaperone	Anxiety, depression
5-HT_{1D}	Agonist	Sumatriptan	Migraine
$5\text{-HT}_{2A/2C}$	Antagonist	Methysergide, risperidone, ketanserin	Migraine, depression, schizophrenia
5-HT_{3}	Antagonist	Ondansetron	Chemotherapy-induced emesis
5-HT_{4}	Agonist	Cisapride	GI disorders
SERT (5-HT transporter)	Inhibitor	Fluoxetine, sertraline	Depression, obsessive-compulsive disorder, panic disorder, social phobia, post-traumatic stress disorder

5-HT receptor agonists

5-HT1A agonist, **buspirone**, is an effective nonbenzodiazepine anxiolytic which does not display the sedative and anticonvulsant properties of benzodiazepines.

Appetite suppression appears to be associated with agonist action at 5-HT2C receptors in the central nervous system, and **dexfenfluramine,** a selective 5-HT agonist, was widely used as an appetite suppressant but was withdrawn because of cardiac valvulopathy. **Lorcaserin,** another 5-HT2C agonist, has recently been approved by the FDA for use as a weight-loss medication.

Cisapride*,* a 5-HT4 agonist, was used in the treatment of gastroesophageal reflux and motility disorders. Because of toxicity, it is now available only for compassionate use in the USA. **Tegaserod**, a 5-HT4 partial agonist, is used for irritable bowel syndrome with constipation.

Compounds such as **fluoxetine** and other SSRIs, which modulate serotonergic transmission by blocking reuptake of the transmitter, are among the most widely prescribed drugs for the management of depression and similar disorders.

5-HT1D/1B Agonists and Migraine

Migraine can usually be distinguished from cluster headaches and tension-type headaches by its characteristics. Migraines present as a pulsatile, throbbing pain, whereas cluster headaches present as excruciating, sharp, steady pain. This is in contrast to tension-type headaches, which present as dull pain, with a persistent, tightening feeling in the head. Patients with severe migraine headaches report 1-5 attacks/month of moderate to severe pain, usually unilateral. The headaches significantly affect quality of life and result in considerable health care costs. Management of headaches involves avoidance of headache triggers (for example, alcohol, chocolate, and stress) and use of abortive treatments for acute headaches, as well as prophylactic therapy in patients with frequent or severe migraines.

Drug	Routes	Time to Onset (h)	Single Dose (mg)	Maximum Dose per Day (mg)	Half-Life (h)
Almotriptan	Oral	2.6	6.25–12.5	25	3.3
Eletriptan	Oral	2	20–40	80	4
Frovatriptan	Oral	3	2.5	7.5	27
Naratriptan	Oral	2	1–2.5	5	5.5
Rizatriptan	Oral	1–2.5	5–10	30	2
Sumatriptan	Oral, nasal, subcutaneous, rectal	1.5 (0.2 for subcutaneous)	25–100 (PO), 20 nasal, 6 subcutaneous, 25 rectal	200	2
Zolmitriptan	Oral, nasal	1.5–3	2.5–5	10	2.8

5-HT receptor antagonists

Ketanserin potently blocks 5-HT2A receptors, less potently blocks 5-HT2C receptors on smooth muscle and other tissues and has little or no reported antagonist activity at other 5-HT.

Ritanserin, another 5-HT2 antagonist, has little or no alpha-blocking action. It has been reported to alter bleeding time and to reduce thromboxane formation, presumably by altering platelet function.

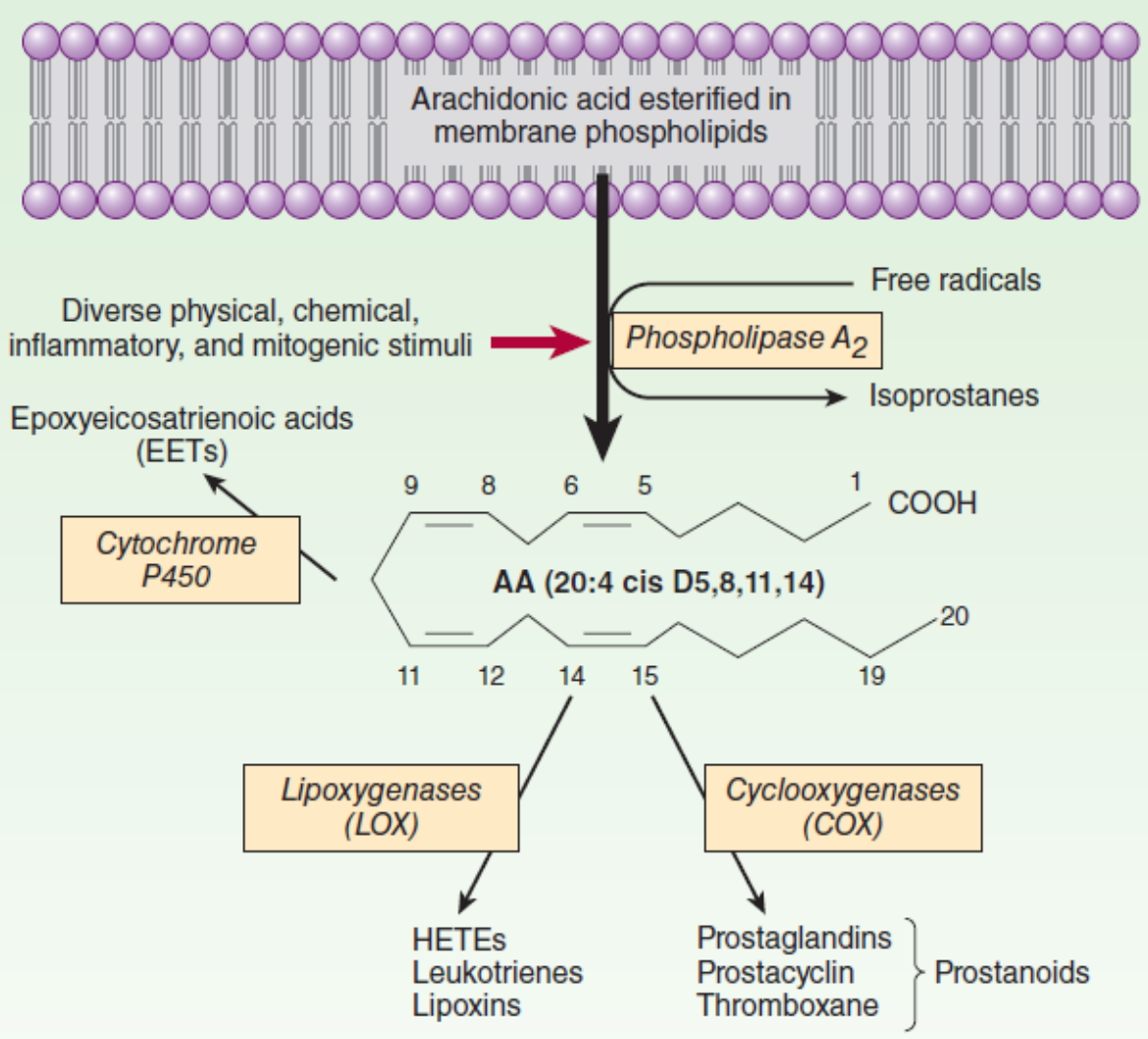
Clozapine, a 5-HT2A/2C antagonist, represents a class of antypical antipsychotic drugs with reduced incidence of extrapyramidal side effects compared to the classic neuroleptics.

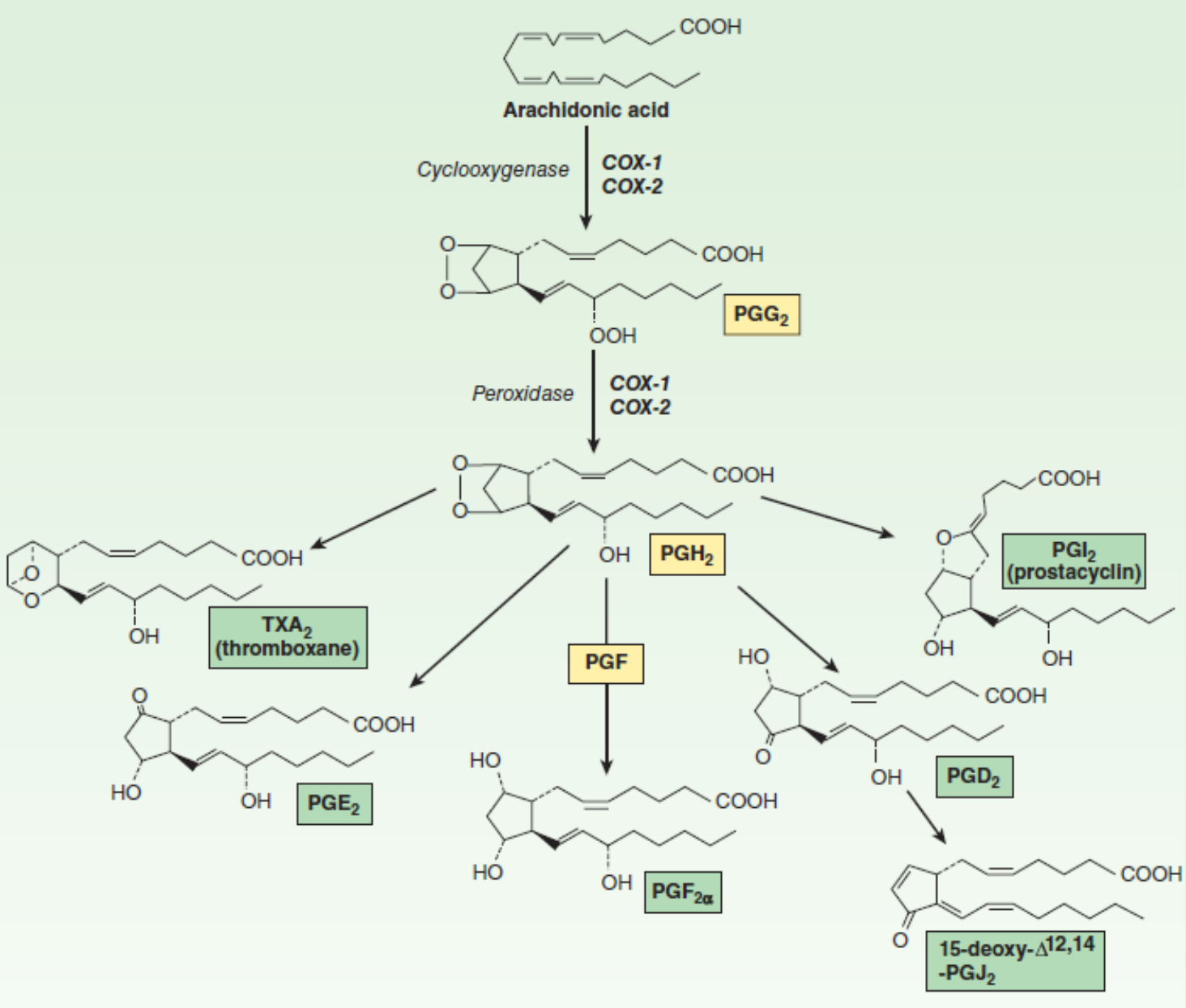
Ondansetron is the prototypical 5-HT3 antagonist. This drug and its analogs are very important in the prevention of nausea and vomiting associated with surgery and cancer chemotherapy.

Prostaglandins

Prostaglandins and related compounds are produced in minute quantities by virtually all tissues. They generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action. Therefore, the prostaglandins do not circulate in the blood in significant concentrations. Thromboxanes and leukotrienes are related lipids that are synthesized from the same precursors as the prostaglandins.

Arachidonic acid is the primary precursor of the prostaglandins and related compounds. Arachidonic acid is present as a component of the phospholipids of cell membranes. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A2 via a process controlled by hormones and other stimuli. There are two major pathways in the synthesis of the eicosanoids from arachidonic acid, the cyclooxygenase and the lipoxygenase pathways.



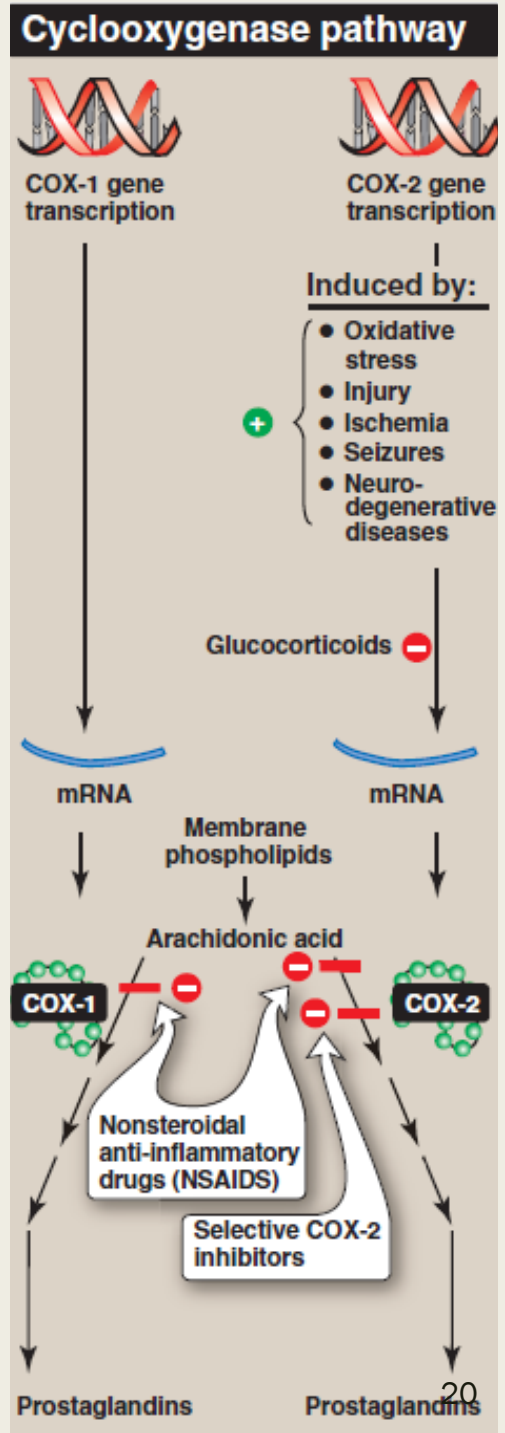

COOH
Arachidonic acid
Cyclooxygenase
COX-1
COX-2
COOH
OOH
PGG2
Peroxidase
COX-1
COX-2
COOH
OH
PGH2
COOH
TXA2
(thromboxane)
OH
COOH
PGI2
(prostacyclin)
OH
OH
PGF
COOH
HO
PGE2
OH
HO
COOH
PGD2
OH
HO
COOH
PGF2α
OH
COOH
15-deoxy-Δ12,14
-PGJ2

Cyclooxygenase pathway: All eicosanoids with ring structures (that is, the prostaglandins, thromboxanes, and prostacyclins) are synthesized via the cyclooxygenase pathway. Two related isoforms of the cyclooxygenase enzymes have been described.

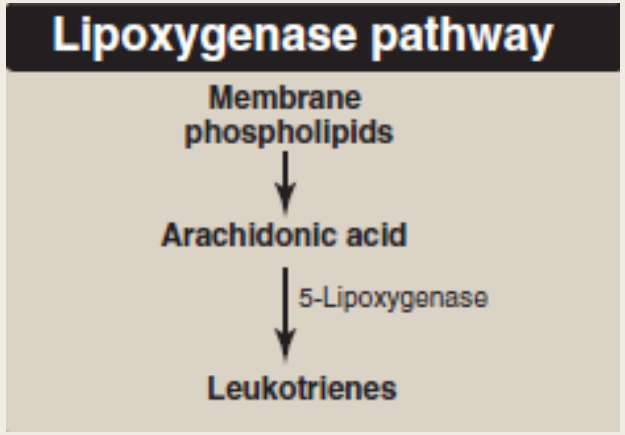
Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostanoids, whereas cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation.

COX-1 is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions.

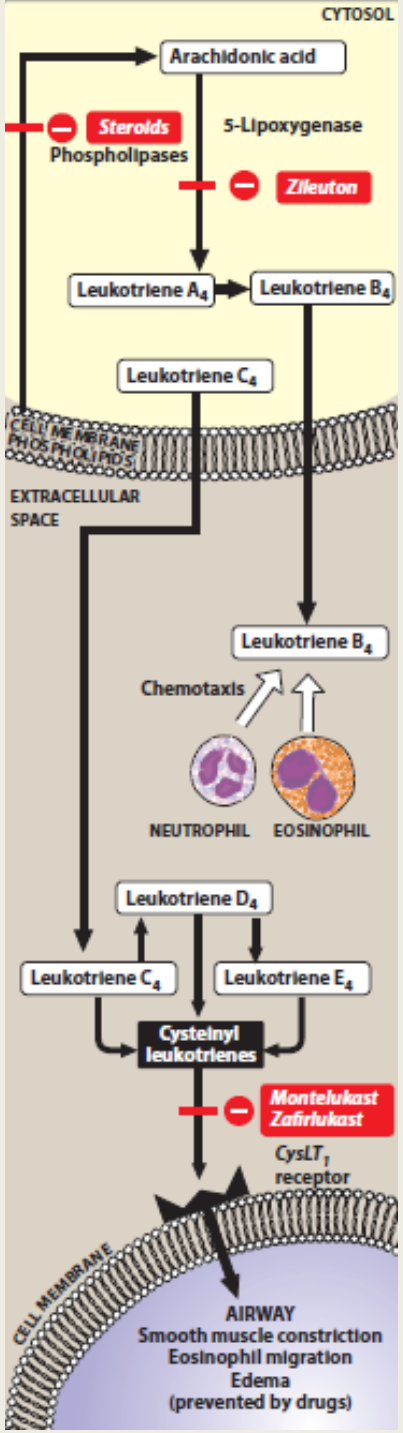
COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone. Its expression at other sites is increased during states of chronic inflammation. Another distinguishing characteristic of COX-2 is that its expression is induced by inflammatory mediators like TNF-α and IL-1 but can also be pharmacologically inhibited by glucocorticoids, which may contribute to the significant anti-inflammatory effects of these drugs.



Lipoxygenase pathway: Alternatively, several lipoxygenases can act on arachidonic acid to form leukotrienes. Antileukotriene drugs, such as *zileuton*, *zafirlukast*, and *montelukast*, are treatment options for asthma.

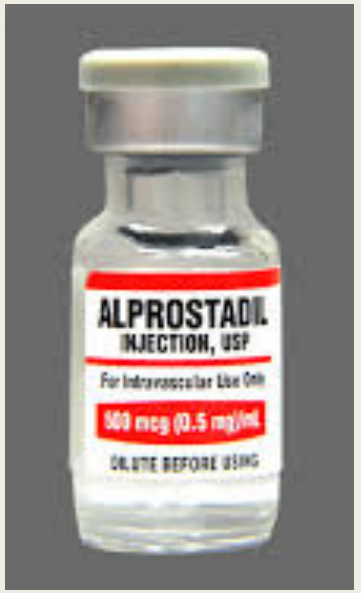


LEUKOTRIENE MODIFIERS	
Montelukast SINGULAIR	Asthma, Allergic rhinitis
Zafirlukast ACCOLATE	Asthma
Zileuton ZYFLO CR	Asthma

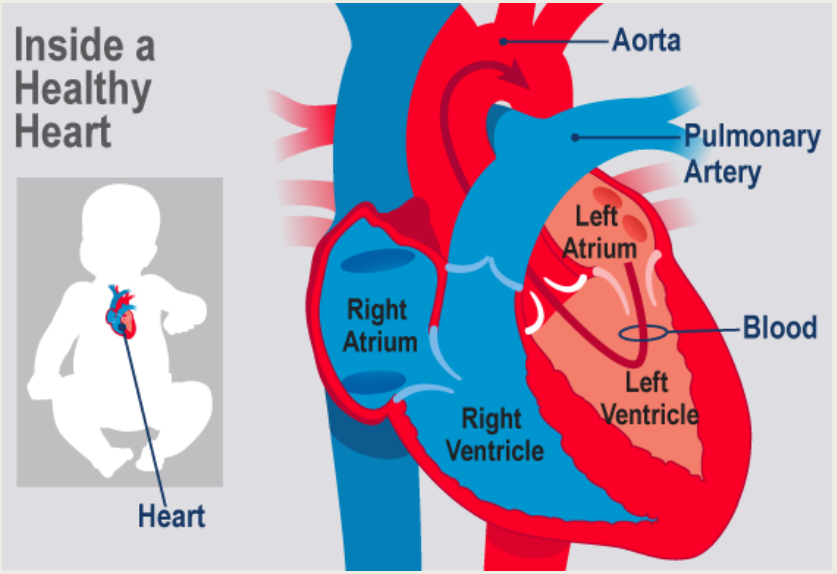


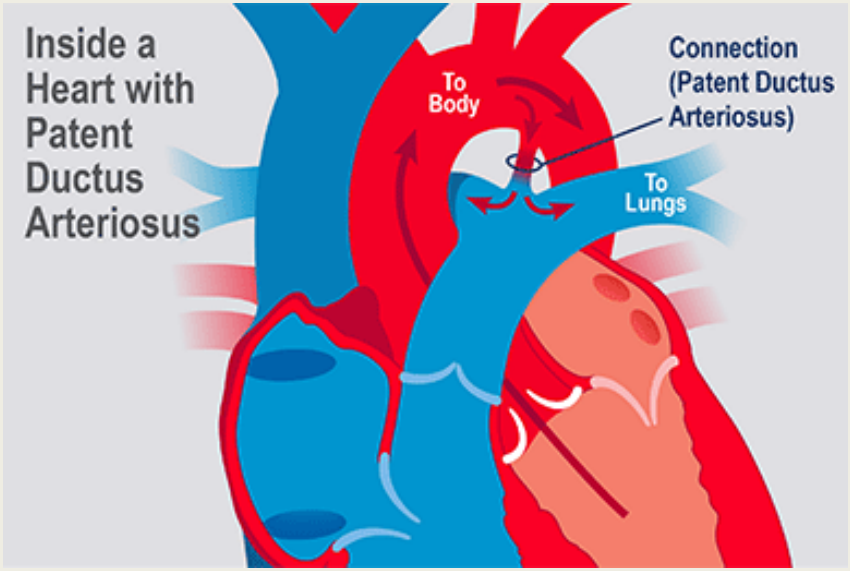
Prostaglandins have a major role in modulating pain, inflammation, and fever. They also control many physiological functions, such as acid secretion and mucus production in the GI tract, uterine contractions, and renal blood flow. Prostaglandins are also among the chemical mediators that are released in allergic and inflammatory processes.

Alprostadil



Alprostadil is a PGE1 that is naturally produced in tissues such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus. Therapeutically, alprostadil can be used to treat erectile dysfunction or to keep the ductus arteriosus open in neonates with congenital heart conditions until surgery is possible. PGE1 maintains the patency of the ductus arteriosus during pregnancy. The ductus closes soon after delivery to allow normal blood circulation between the lungs and the heart. Infusion of the drug maintains the ductus open as it naturally occurs during pregnancy, allowing time until surgical correction is possible.



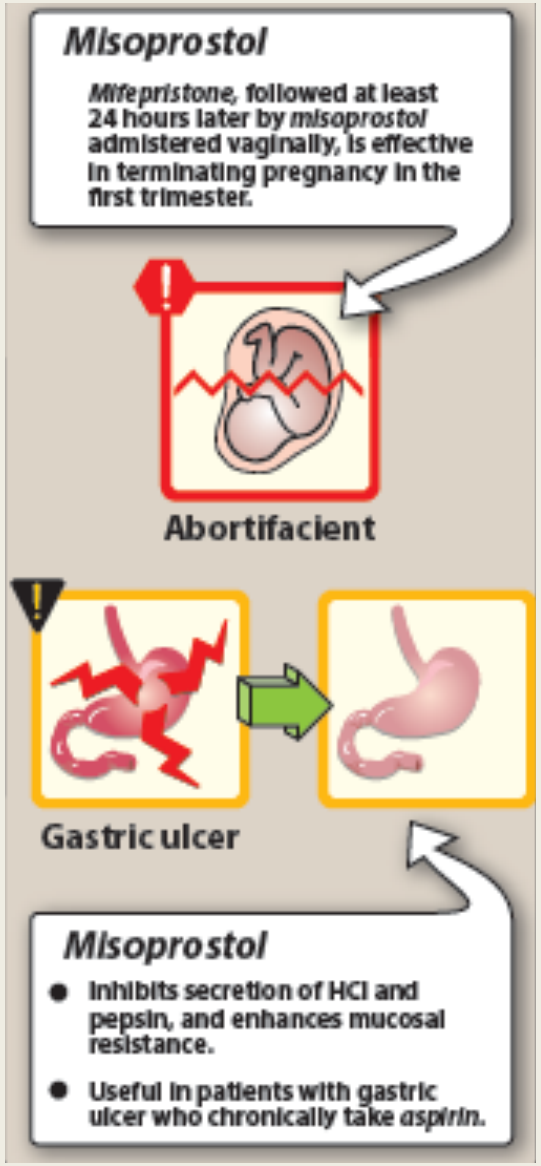


Lubiprostone

Lubiprostone is a PGE1 derivative indicated for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation. It stimulates chloride channels in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion. Nausea and diarrhea are the most common side effects of *lubiprostone*. Nausea can be decreased if taken with food. Drug-drug interactions appear minimal because metabolism occurs quickly in the stomach and jejunum.

Misoprostol

Misoprostol, a PGE1 analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment. Misoprostol interacts with prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion. Furthermore, misoprostol has a GI cytoprotective effect by stimulating mucus and bicarbonate production. This combination of effects decreases the incidence of gastric ulcers caused by NSAIDs. Misoprostol is also used off-label in obstetric settings for labor induction, since it increases uterine contractions by interacting with prostaglandin receptors in the uterus. Misoprostol has the potential risk to induce abortion in pregnant women. Therefore, the drug is contraindicated during pregnancy. Its use is limited by common side effects including diarrhea and abdominal pain.



Prostaglandin F2α analogs

Bimatoprost, latanoprost, tafluprost and travoprost are PGF2α analogs that are indicated for the treatment of open-angle glaucoma. By binding to prostaglandin receptors, they increase uveoscleral outflow, reducing intraocular pressure. They are administered as ophthalmic solutions once a day and are as effective as timolol or better in reducing intraocular pressure. Bimatoprost increases eyelash prominence, length, and darkness and is approved for the treatment of eyelash hypotrichosis. Ocular reactions include blurred vision, iris color change (increased brown pigmentation), increased number and pigment of eyelashes, ocular irritation, and foreign body sensation.

Cholinergic agonists (topical)	*Pilocarpine, carbachol*	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision.
Prostaglandin-like analogues (topical)	*Latanoprost, travoprost, bimatoprost*	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.

Prostacyclin (PGI2) analogs

Epoprostenol, the pharmaceutical form of naturally occurring prostacyclin, and the synthetic analogs of prostacyclin (iloprost and treprostinil) are potent pulmonary vasodilators that are used for the treatment of pulmonary arterial hypertension. These drugs mimic the effects of prostacyclin in endothelial cells, producing a significant reduction in pulmonary arterial resistance with a subsequent increase in cardiac index and oxygen delivery. These agents all have a short half-life. Epoprostenol and treprostinil are administered as a continuous intravenous infusion, and treprostinil may also be administered orally or via inhalation or subcutaneous infusion. Inhaled iloprost requires frequent dosing due to the short half-life. Dizziness, headache, flushing, and fainting are the most common adverse effects. Bronchospasm and cough can also occur after inhalation of iloprost.