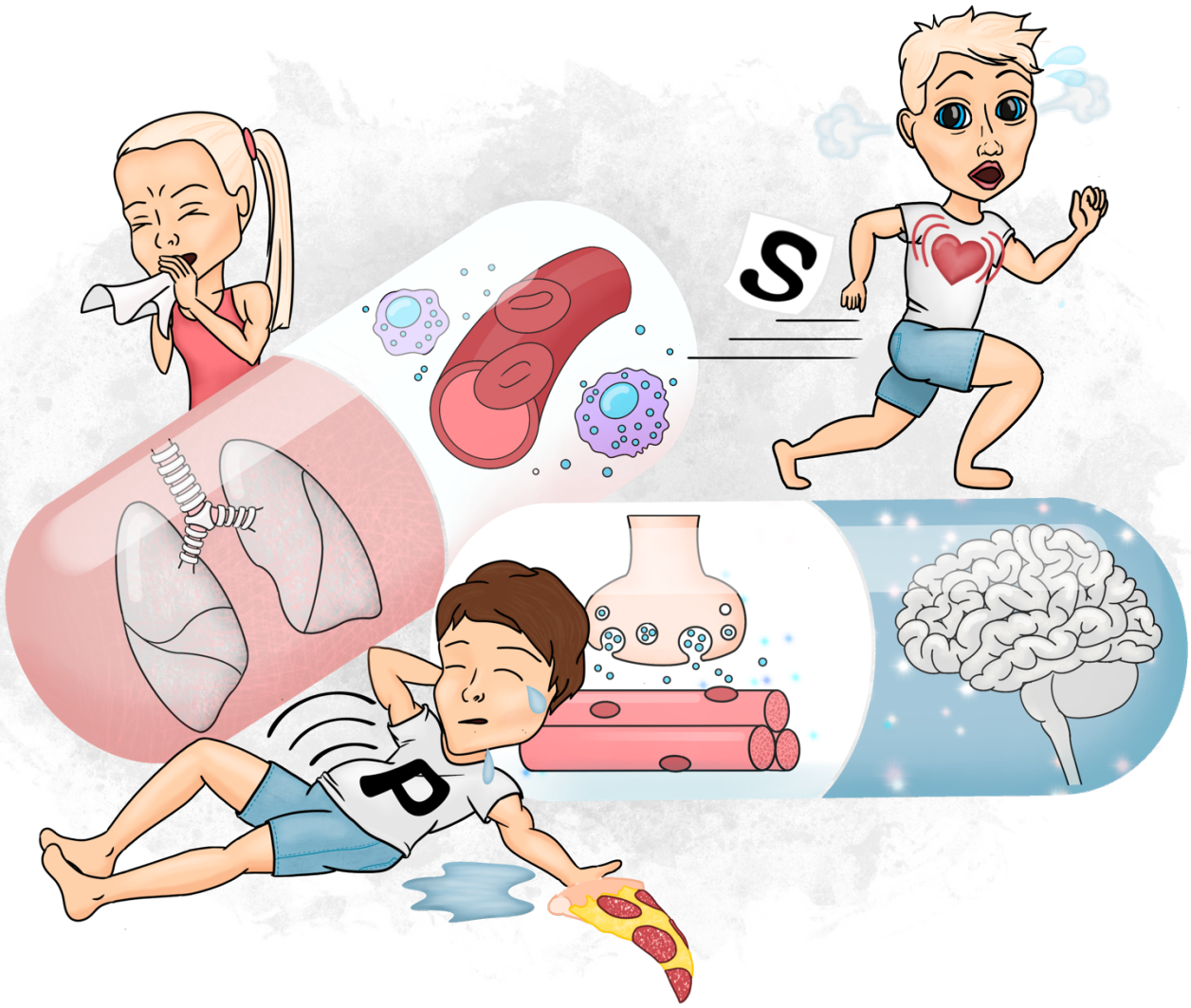

Pharmacology Exam 1

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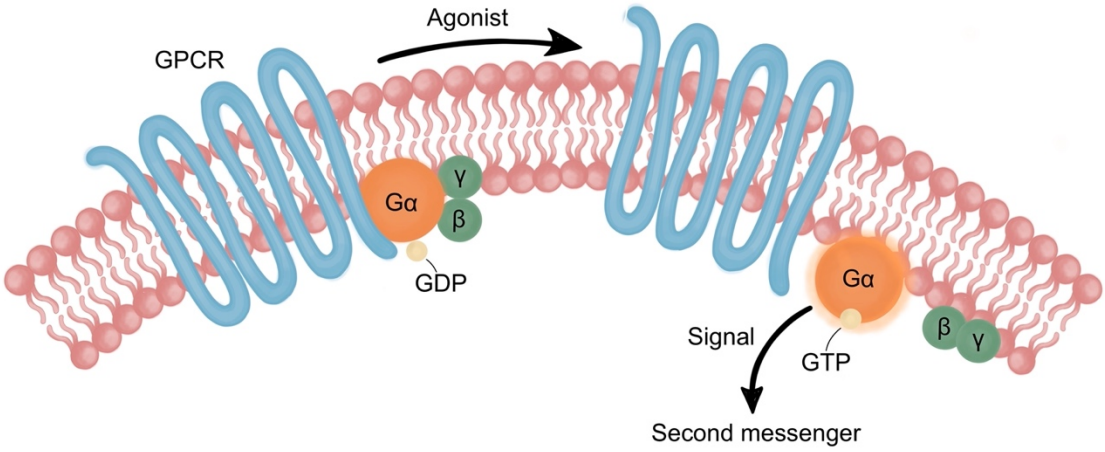
Section 1 – Cell Signaling

1.1 – G Protein-Coupled Receptors (GPCR)



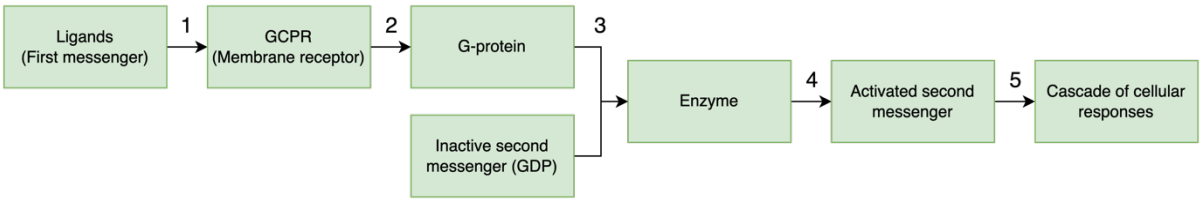
1.1.1 – Mechanism

- G protein-coupled receptors are membrane receptors which are commonly used as the target in modern medicinal drugs.
- GPCR interact with G-proteins, which consist of three subunits; alpha, beta and gamma.
- Both the alpha subunit and the beta-gamma dimer can relay messages inside the cell, by targeting specific enzymes producing various second messengers

1.1.2 – Examples of G Protein-Coupled Receptors

- Muscarinic receptors
- Adrenergic receptors
- Histamine receptors
- Serotonin receptors
- Endothelin receptors
- Dopamine receptors

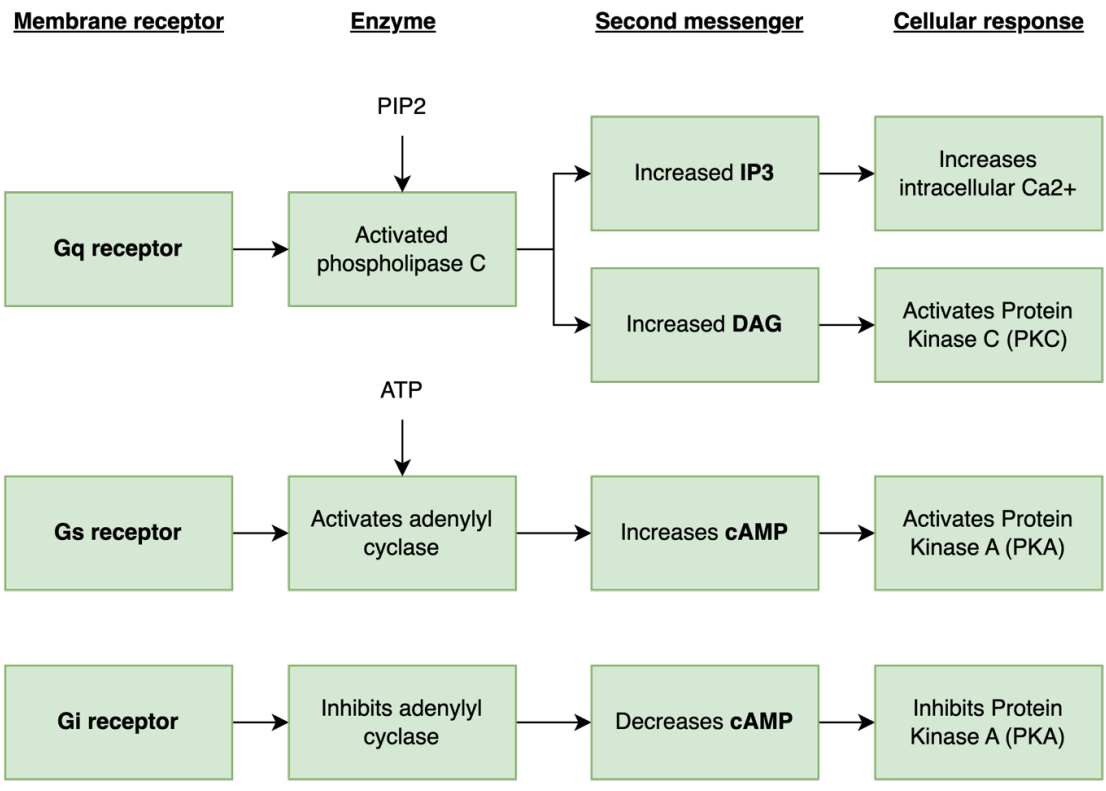
1.2 – Cell Signaling Cascade



1. Ligands (first messengers) are extracellular signaling molecules that attach to the G protein-coupled receptors (membrane receptor) on the cell
2. As a result, GPCR undergo a conformational change and interact with the G-protein
3. Leads the alpha subunit of the G-protein to exchange GDP for GTP, and then dissociate from the beta and gamma sub unit
4. Alpha subunit (and, to a lower extent, the beta-gamma dimer) then activates other signaling molecules in the cells by targeting specific enzymes
5. The second messenger mediates a cascade of cellular responses

1.3 – Second Messengers

- Second messengers are intracellular signaling molecules that relay signals after being activated by first messengers
- cAMP, IP3 and DAG are important second messengers that are activated by different G protein-coupled receptors



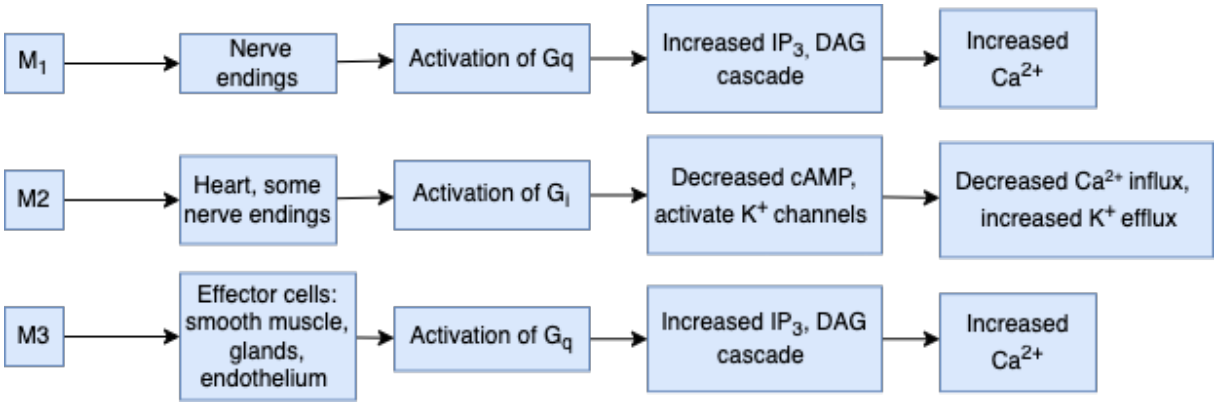
Section 2 – ANS receptors

2.1 – Cholinoceptors

Also referred to as cholinergic receptors. These are receptors that react to acetylcholine and its analogs.

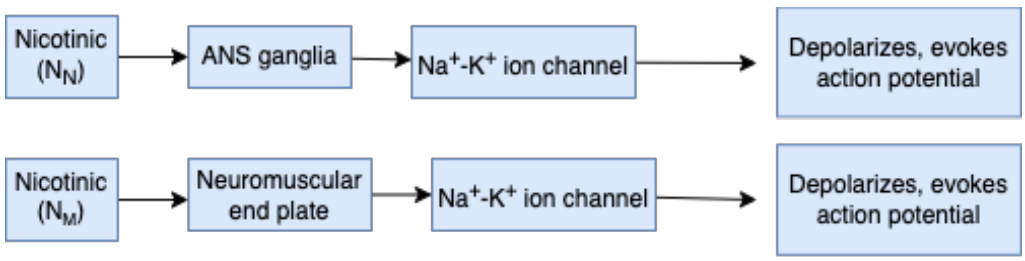
2.1.1 – Muscarinic Receptors

- Responds to the alkaloid muscarine, as well as acetylcholine and its derivatives.
- Found in smooth muscle, cardiac tissue, and glands at parasympathetic neuroeffector junctions.
- All are G-protein-coupled receptors.



2.1.2 – Nicotinic Receptors

- Located on Na^+-K^+ ion channels.
- Responds to acetylcholine and nicotine (another acetylcholine mimic) by opening these channels.
- Located in ganglia and skeletal muscle end plates.

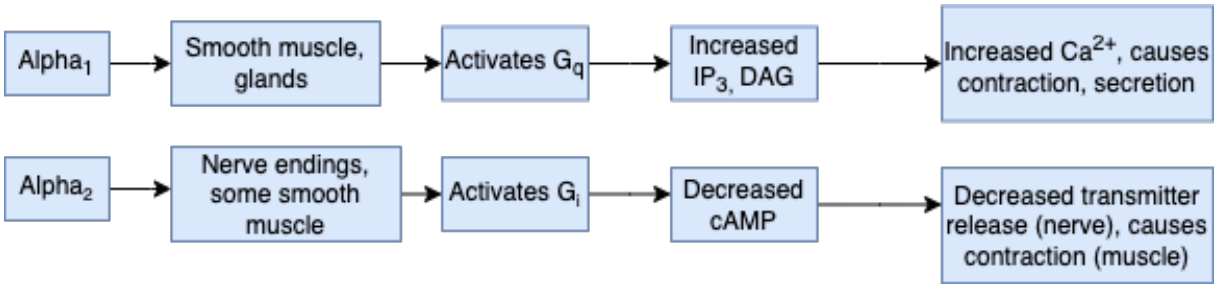


2.2 – Adrenoceptors

Also referred to as adrenergic receptors. These are receptors that react to norepinephrine and epinephrine.

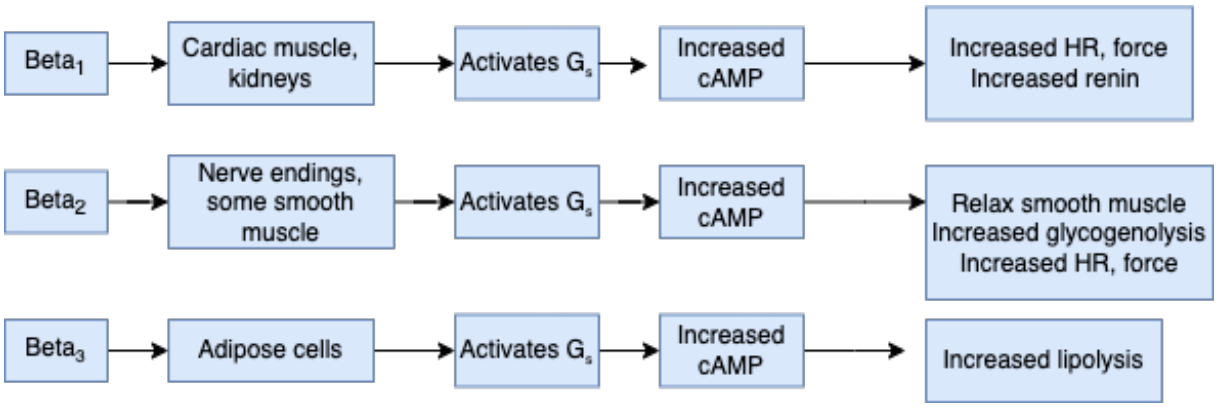
2.2.1 – Alpha Receptors

- Subdivided into α_1 and α_2.
- Use different G-coupling proteins.
- Located on vascular smooth muscle, presynaptic nerve terminals, blood platelets, fat cells, and neurons in the brain.



2.2.2 – Beta Receptors

- Subdivided into β_1, β_2 and β_3.
- Use the same G-coupling protein.
- Located on most types of smooth muscle, lipocytes and some presynaptic nerve terminals.



2.3 – Dopamine Receptors

- Subclass of adrenoceptors.
- Important in renal and splanchnic vessels, and in the brain.
- The D_1 subtype appears to be the most important one on peripheral effector cells.
- The D_2 receptors are found on presynaptic nerve terminals.

2.4 – Test Yourself

1) Where are typically muscarinic M_1 receptors found?

a) Lungs and heart
b) Nerve endings
c) CNS
d) Smooth muscles

2) Which neurotransmitter do adrenergic receptors react to?

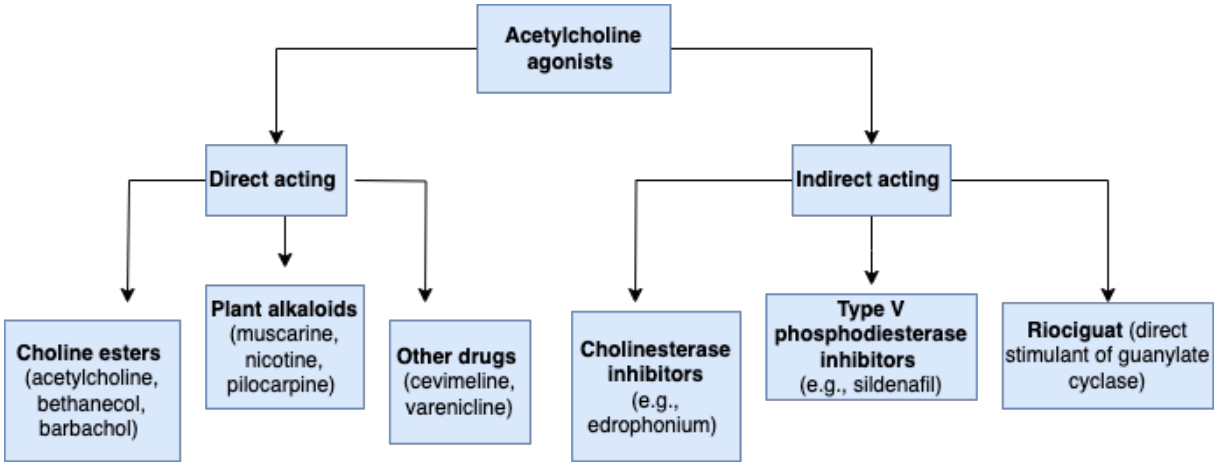
a) Acetylcholine
b) Nicotine
c) Epinephrine
d) Muscarine

3) How many subtypes of α receptors exist?

a) α_1,α_2 and α_3
b) α_1 only
c) α_1 and α_2
d) α_2 only

Section 3 – Acetylcholine Drugs

3.1 – Overview of Acetylcholine Agonists



3.2 – Direct-Acting Acetylcholine Receptor Agonists

3.2.1 – Choline Esters

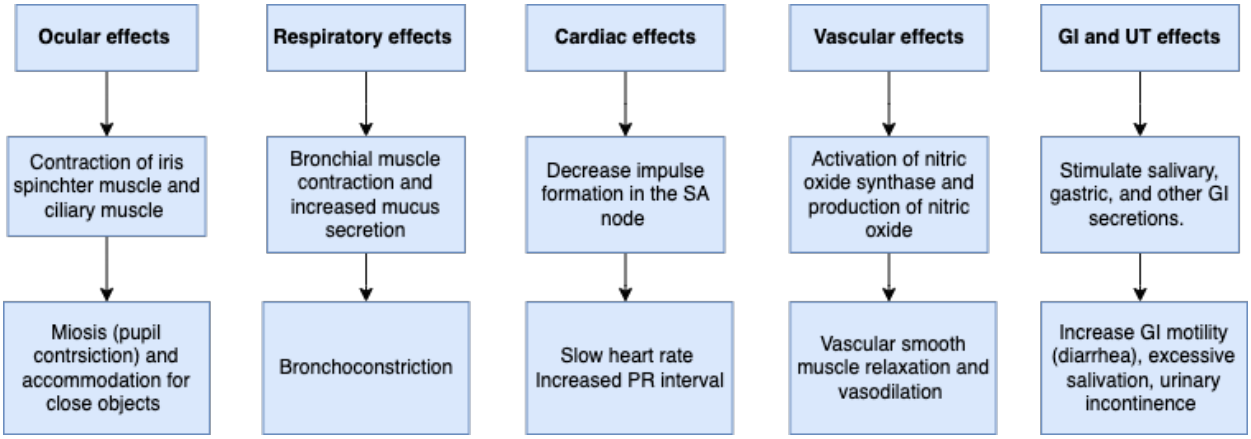
I. Drugs

- Poorly absorbed from the GI tract, and not distributed to the CNS.

	Receptor specificity	Duration of action	Route of administration	Clinical use
Acetylcholine	Muscarinic and nicotinic	Seconds	Intraocular	Miosis during ophthalmic surgery
Bethanechol	Muscarinic	Hours	Oral Subcutaneous	GI and urinary stimulation
Carbachol	Muscarinic and nicotinic	Hours	Intraocular	Miosis during ophthalmic surgery

II. Side Effects

- Due to their lack of specificity, the choline esters cause a variety of effects on many organs.
- These side effects are typical for all cholinergic agonists.



CLINICAL CORRELATION

Asthma

Muscarinic receptor agonists cause bronchoconstriction. Therefore, they should be avoided in or used with extreme caution in patients with obstructive lung diseases, like asthma.

3.2.2 – Plant Alkaloids

- Includes **muscarine**, **nicotine**, and **pilocarpine**.
- Muscarine is found in mushrooms, and consumption of these can cause diarrhea, sweating, salivation, and lacrimation.
- Pilocarpine is obtained from *Pilocarpus*, a type of shrub. Has greater affinity for the muscarinic receptors than for nicotinic receptors.

CLINICAL CORRELATION

Pilocarpine

- Is a second-line drug in the treatment of chronic open-angle glaucoma.
- It lowers intraocular pressure by increasing the outflow of aqueous humor.

3.2.3 – Other Muscarinic Agonists

	Receptor	Clinical use
Cevimeline	M3 selective	Sjögren syndrome (dry eyes, mouth, and arthritis)
Varenicline	Partial agonist of nicotinic receptors in CNS	Smoking cessation

3.3 – Indirect-Acting Acetylcholine Receptor Agonists

- The indirect-acting agonists include the cholinesterase inhibitors, type V phosphodiesterase inhibitors and Riocugurat (a guanylate cyclase stimulator).

3.3.1 – Cholinesterase Inhibitors

- Cholinesterase is an enzyme that break down acetylcholine.
- Cholinesterase inhibitors decrease the breakdown of acetylcholine at all cholinergic synapses, thus increase the amount of acetylcholine in the synapse.

I. Reversible Cholinesterase Inhibitors

	Mechanism	Duration	Clinical use	Crosses blood-brain barrier
Edrophonium	Prevents the hydrolysis of acetylcholine by cholinesterase	10 min	Myasthenia gravis (diagnosis)	No
Neostigmine		2-4 hours (PO, IM, SC) 2-5 min (IV)	Myasthenia gravis Reversal of curariform drugs	No
Pyridostigmine		3-6 hours (PO) 2-5 min (IV), 15 min (IM)	Same as neostigmine	No
Physostigmine		1-5 hours (IV, IM)	Reversal of CNS effects of antimuscarinic drugs	Yes

CLINICAL CORRELATION

Edrophonium

- Edrophonium is a cholinesterase inhibitor used in the diagnosis of myasthenia gravis.
- Myasthenic crisis is a condition in myasthenia gravis where there is decreased acetylcholine transmission, whereas in cholinergic crisis there is increased transmission. Both conditions are characterized by muscle weakness and paralysis.
- A patient receiving edrophonium while in myasthenic crisis will improve, whereas a patient in cholinergic crisis will not improve.

Cholinergic crisis

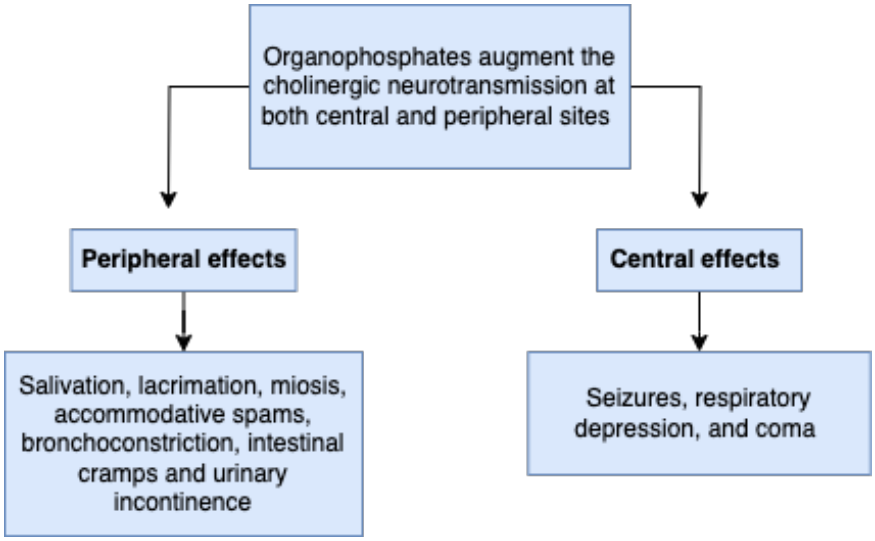
The muscle weakness is caused by an excessive amount of acetylcholine at the junction. This causes depolarization neuromuscular blockade.

Myasthenic crisis

Patient is not receiving adequate doses of the drug, and the muscle weakness is caused by acetylcholine deficiency.

II. Longer-Acting Cholinesterase Inhibitors

- Also referred to as quasireversible cholinesterase inhibitors.
- Are all organophosphate compounds.
- Most of them are used as pesticides. Therefore, they are responsible for cases of accidental and intentional poisoning.
- Most of them are highly lipid soluble. This makes them effectively absorbed from all sites in the body (skin, mucous membranes, and gut).
- **Malathion** is a pesticide which is also used to treat head lice.



CLINICAL CORRELATION

Management organophosphate poisoning

1) Decontamination of the patient
2) Support of cardiovascular and respiratory functions
3) Atropine
   - Acetylcholine receptor antagonist
   - Blocks excessive acetylcholine stimulation.
4) Pralidoxime
   - Regenerates cholinesterase
   - Particularly helpful in reducing nicotinic receptor stimulation.

III. Centrally Acting Cholinesterase Inhibitors

- Cholinesterase Inhibitors which cross the blood-brain-barrier.
- Drugs include donepezil, galantamine and rivastigmine.
- Used in Alzheimer's disease, covered in pharmacology booklet 2.

3.3.2 – Type V Phosphodiester Inhibitors

SUFFIX-

Type V Phosphodiesterase Inhibitors: -afil

I. Drugs

- Potentiate the vasodilation effect of acetylcholine.
- All are used for erectile dysfunction in men.

	Half-life	Duration	Absorption	Clinical use
Sildenafil	4 hours	4-6 hours	Decreased by high-fat meal	Erectile dysfunction Pulmonary arterial hypertension
Tadalafil	17 hours	36 hours		Erectile dysfunction Benign prostatic hyperplasia (BPH) Pulmonary arterial hypertension
Vardenafil	4 hours	4-6 hours		Erectile dysfunction
Avanafil				Erectile dysfunction

II. Side effects

- Side effects of type V phosphodiesterase inhibitors are usually mild.
- They include headache, nasal congestion, visual disturbance, back pain, and dyspepsia.
- Lowers the blood pressure by 7-8 mmHg.
- Should not be used in combination with nitroglycerin. This can cause profound hypotension and reflex tachycardia.

3.3.3 – Riociguat

- New drug for treating pulmonary arterial hypertension.
- It is a cyclic GMP stimulator.

3.4 – Acetylcholine Receptor Antagonists

- These are drugs that selectively block the muscarinic or nicotinic receptors.

3.4.1 Muscarinic Antagonists

- These drugs compete with acetylcholine for its receptors. They therefore inhibit the effects of parasympathetic nerve stimulation.

I. Effects of muscarinic antagonists

- There are selective and non-selective antimuscarinic drugs.
- Pirenzepine and telenzepine are selective M_1 antagonists.
- Most of the antimuscarinic drugs in use are relatively non-selective.

Organ	Examples of drugs	Effect	Mechanism	Clinical uses
CNS	Scopolamine Benztropine, biperiden and trihexyphenidyl	Sedation, anti-motion sickness action, anti-Parkinson action, delirium	Block of muscarinic receptors, several types	Therapy of motion sickness Parkinsonism[1]
Eye	Atropine Homatropine Cyclopentolate Tropicamide	Cycloplegia, mydriasis	Block of M_3 receptors	Used to dilate pupil and prevent accommodation
Bronchi	Ipratropium Tiotropium Aclidinium	Bronchodilation	Block of M_3 receptors	Asthma and COPD
GI	Pirenzepine	Relaxation, slowed peristalsis, reduced salivation	Block of M_1 receptor	Peptic ulcer Muscle cramps
Bladder	Oxybutynin Tolterodine Darifenacin	Relaxation of bladder wall, urinary retention	Block of M_3 and possibly M_1 receptors	Reduce urgency and bladder spasms

[1]Benztropine, biperiden and trihexyphenidyl (drugs used in Parkinson) are not as effective av levodopa, but they are used in adjuncts or when patients become unresponsive to levodopa.

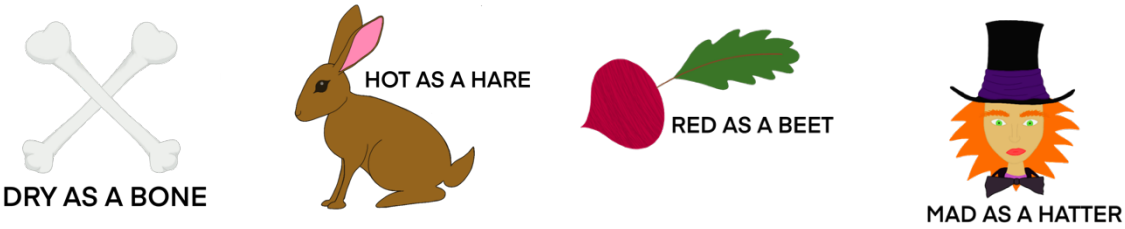
CLINICAL CORRELATION

Scopolamine and atropine

- People with darker irises bind more of the drug and experience a longer duration than people with lighter irises.
- This is because they bind to pigments in the iris that slowly release the drugs.

II. Toxicities of muscarinic antagonists

- A mnemonic useful to remember the side effects of atropine: “Dry as a bone, hot as a hare, red as a beet, mad as a hatter.”
- Salivation, sweating, and lacrimation are all significantly reduced or stopped in atropine toxicity (“dry as a bone”).
- Hyperthermia is caused by reduced sweating. This can be especially dangerous in small children and infants (“hot as a hare”).
- Dilation of cutaneous vessels can lead to flushing (“red as a beet”).
- CNS toxicity includes sedation, amnesia, and delirium or hallucinations (“mad as a hatter”).
- Treatment Is usually symptomatic, but severe tachycardia may require small doses of physostigmine (cholinesterase inhibitor).



3.4.2 – Neuromuscular Blocking Agents

- Bind to the muscle type of nicotinic acetylcholine receptors and inhibit neurotransmission at skeletal neuromuscular junctions.
- This causes muscle weakness and paralysis.

I. Non-depolarizing vs depolarizing NMB

	Mechanism	Action	Clinical use
Non-depolarizing neuromuscular blocking agents	Competitive antagonists of Ach at nicotinic receptors in skeletal muscle. Stimulate histamine release from mast cells.	Cause paralysis. Bronchoconstriction Tachycardia Hypotension	Muscle relaxation during surgery.
Depolarizing neuromuscular blocking agents	Persistent depolarization at the motor end plate	Produces fasciculations[1], followed by sustained muscle paralysis	Muscle relaxant during surgery. Facilitate intubation of airway.

[1]Fasciculations are transient muscle contractions.

II. Drugs

	Depolarizing agents	Effects reversed by cholinesterase inhibitors	Duration of action (minutes)
Succinylcholine	Yes	No	Short (5-10)
Atracurium	No	Yes	Intermediate (30-60)
Cisatracurium			Intermediate (30-60)
Pancuronium			Long (60-120)
Rocuronium			Intermediate (30-60)
Vecuronium			Intermediate (30-60)

3.5 - Test Yourself

1) How do muscarinic receptor agonists effect the respiratory system?

_____

_____

_____

2) What is the clinical use of pilocarpine?

a) Acute closed angle glaucoma
b) Excessive sweating
c) Constipation
d) Chronic open angle glaucoma

3) Which one of these cholinesterase inhibitors cross the blood-brain-barrier?

a) Edrophonium
b) Physostigmine
c) Pyridostigmine
d) Neostigmine

4) Explain the difference between a myasthenic crisis and a cholinergic crisis.

_____

_____

_____

5) Which of these can be used in organophosphate poisoning?

a) Pilocarpine
b) Edrophonium
c) Atropine
d) Muscarine

4.1 – Adrenergic agonists

- These drugs are valuable in treating a wide range of clinical conditions. Ranging from cardiovascular conditions to the common cold. They act by stimulating α and β receptors.

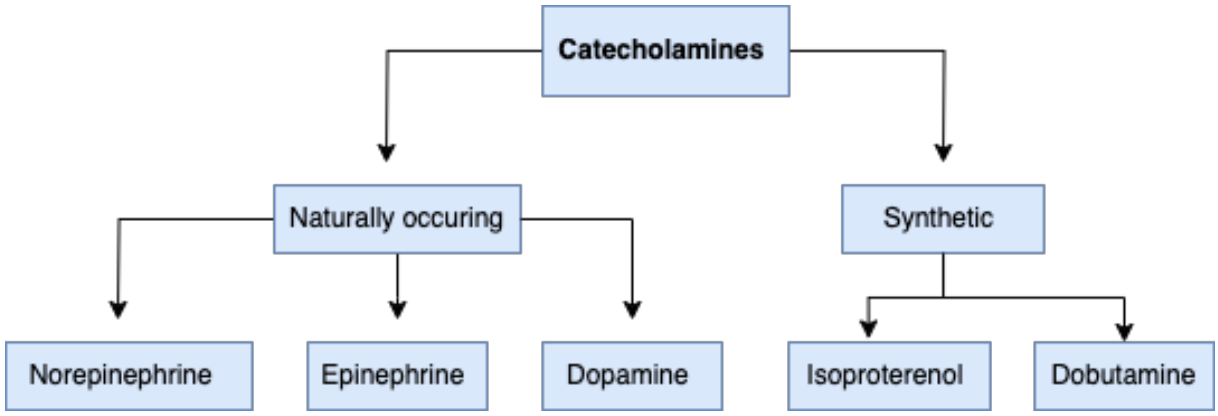
4.1.1 – Receptors

Adrenoceptors	Mechanism	Location	Effects
α_1	Phospholipase C activation → ↑ $IP3_3$ and release of Ca^{2+}	Vascular smooth muscle Pupillary dilator muscle Exocrine glands CNS	Vasoconstriction Mydriasis Increased closure of internal sphincter of the bladder. Increased peripheral resistance. Increased blood pressure
α_2	Inhibit adenylyl cyclase → ↓ cAMP	Blood platelets Various tissues	Platelet aggregation ↓ in secretion of aqueous humor ↓ in secretion of insulin Inhibit release of NE[1]
β_1	Activate adenylyl cyclase → ↑ cAMP → Protein kinase activation	Cardiac tissue Juxtaglomerular apparatus	↑ heart rate, contractility, and conduction ↑ renin release
β_2	Activate adenylyl cyclase → ↑ cAMP → Protein kinase activation	Bronchi, uterus, vascular smooth muscle Liver	Relaxation of smooth muscle (vasodilation and bronchodilation) Uptake of K^+ to skeletal muscle Glycogenolysis
β_3	Activate adenylyl cyclase → ↑ cAMP → Protein kinase activation	Adipose tissue	Lipolysis

[1]NE: Norepinephrine

4.1.2 – Catecholamines

- Catecholamines are a type of neurohormone, and they are important in stress responses.

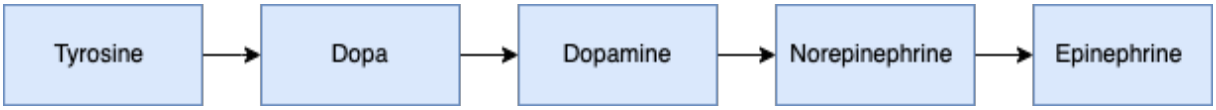


I. Pharmacokinetics

- Catecholamines are rapidly inactivated by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). These are enzymes that degrade catecholamines.
- Due to these enzymes, catecholamines have short half-lives and a low oral bioavailability.

II. Synthesis of catecholamines

- The catecholamines dopamine, norepinephrine and epinephrine are synthesized from dietary tyrosine.



III. Direct-acting catecholamines

- Epinephrine: potent agonist at all α and β adrenoceptors
- Norepinephrine: $\alpha = \beta_1 > \beta_2$
- In other words, norepinephrine differs from epinephrine only in that norepinephrine constricts all blood vessels, whereas epinephrine constricts some and dilates others.

CLINICAL CORRELATION

Epinephrine

At low doses, β effects (vasodilation) in the vascular system predominate.

At high doses, α effects (vasoconstriction) are the strongest.

	Action	Clinical use	Adverse effects	Receptor specificity
Epinephrine	↑ Heart rate[1] and contractility[2] ↑ Renin release Increased pulse pressure. Bronchodilation (β_2 action). Hyperglycemia Lipolysis	Bronchospasms Anaphylactic shock Cardiac arrest Anesthetics[3]	CNS effects (anxiety, fear, tremor) Arrhythmias	α_1, α_2 β_1, β_2
Norepinephrine	Vasoconstriction Increased blood pressure	Shock	Like epinephrine.	α_1, $\alpha_2 > \beta_1$
Isoproterenol	↑ Heart rate, contractility, and CO Bronchodilation	AV block Bradycardia	Tachycardia	β_1, β_2
Phenylephrine	Vasoconstriction Increases blood pressure	Hypotension Nasal decongestant		α_1
Dobutamine	↑ Heart rate, contractility, and CO.	Acute heart failure Inotropic support after cardiac surgery	Atrial fibrillation	β_1

[1] Positive inotrope (β_1 action) = increased contractility of the heart

[2] Positive chronotrope (β_1 action) = increased heart rate

[3] Local anesthetics may contain low concentrations of epinephrine. This produces vasoconstriction at side of injection.

IV. Indirect-acting agonists

- Agents that increase the concentration of NE.
- An example of an indirect-acting agonists that inhibit the reuptake of NE is cocaine.
- An example of an indirect-acting agonist that increase the release of NE is amphetamines.
- These drugs are covered in booklet 2.

4.2 – Adrenergic Antagonists

- Include drugs that block α-adrenoceptors and β-adrenoceptors.

4.2.1 - α-Adrenergic Blocking Agents

- These drugs primarily affect blood pressure.

	Action	Clinical use	Adverse effects	Receptor specificity
Phenoxy-benzamine	Prevents vasoconstriction. Epinephrine reversal of α stimulation.	Pheochromocytoma. Raynaud disease and frostbite.	Orthostatic hypotension. Nasal stuffiness. Reflex tachycardia.	Non-selective
Phentolamine	Like phenoxybenzamine but has shorter duration.	Short-term management of pheochromocytoma. Hypertensive crisis.	Like phenoxybenzamine.	Non-selective
Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin	Decrease peripheral vascular resistance.	Hypertension Benign prostatic hyperplasia	Orthostatic hypotension	Selective for α_1 receptor.
Yohimbine	Works at the level of CNS to increase sympathetic outflow.	Erectile dysfunction.	May worsen psychiatric conditions and renal dysfunction.	Selective for α_2 receptor.

4.2.2 - β-adrenergic Blocking Agents

- All β-blockers lower blood pressure, but they do not induce orthostatic hypotension. This is because the α-adrenoreceptors remain functional.

	Receptor specificity	Clinical use	Duration of action	Effects
Propranolol	Non-selective, β_1, β_2	Hypertension Migraine Hyperthyroidism MI	4-6 hours	Decreases heart rate, CO, O2 demand, AV node conduction and blood pressure
Nadolol **Pindolol**	Non-selective, β_1, β_2	Hypertension	Nadolol – 14-24 hours Pindolol – 3-4 hours	Same as propranolol
Timolol	Non-selective, β_1, β_2	Glaucoma Hypertension	4-6 hours	Same as propranolol; also decreases intraocular pressure
Atenolol **Bisoprolol** **Esmolol** **Metoprolol**	Selective β_1	Hypertension Angina MI	Esmolol – 10 minutes Metoprolol – 3-4 hours	Same as propranolol
Acebutolol	Selective β_1	Hypertension	3-4 hours	Same as propranolol
Nebivolol	Selective β_1, ↑NO	Hypertension	10-30 hours	Same as propranolol
Carvedilol **Labetalol**	Non-selective, α_1,β_1, β_2	Hypertension	Carvedilol – 7-10 hours Labetalol – 4-6 hours	Causes vasodilation; decreases heart rate and blood pressure

MNEMONIC!

β_1-cardioselective β-blockers
MAN BABE

Metoprolol
Atenolol
Nebivolol
Bisoprolol
Acebutolol
Betaxolol
Esmolol

4.3 – Test Yourself

1) Which dietary amino acid is norepinephrine derived from?

_____

_____

2) Which statement is correct?

a) At low doses epinephrine causes more vasoconstriction (α effects) than vasodilation (β effects).
b) At low doses epinephrine causes more vasodilation (β effects) than vasoconstriction (α effects).
c) At high doses of epinephrine, vasodilation predominates.
d) At low doses of epinephrine, vasoconstriction predominates.

3) What does it mean when a drug has positive inotropic effects?

_____

_____

_____

4) What does it mean when a drug has positive chronotropic effects?

_____

_____

_____

5) Which of these findings would most likely be seen in a person who has taken alpha blockers?

a) Bradycardia
b) Tachycardia
c) High blood pressure
d) Nothing

6) Name the selective beta-blockers.

_____

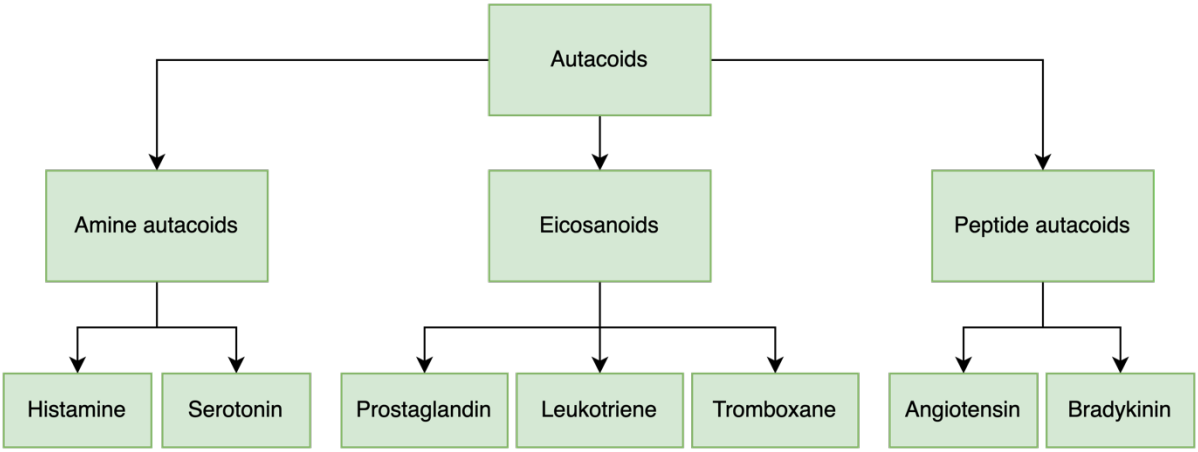
_____

_____

Section 5 – Autacoids

5.1 – General About Autacoids

- Autacoids are local mediators or "hormones" of acute inflammation. They are locally produced and have local effects.
- Acts on smooth muscles, nerves, glands, platelets, and other tissues.
- Autacoids are divided into three main classes shown in the flow chart below.



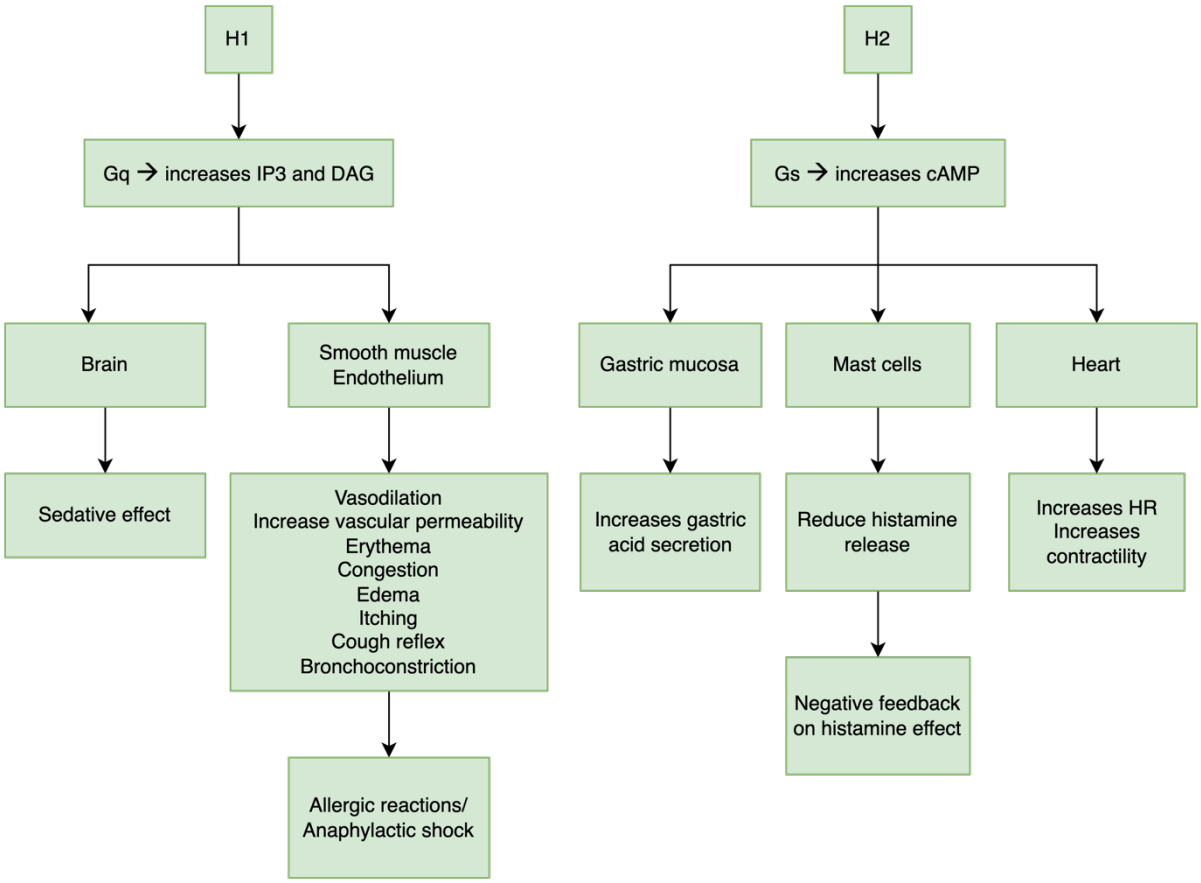
5.2 – Histamine

- Histamine is an important mediator of the inflammatory and allergic response.
- Produced by mast cells or basophils in response to injury, and are released when they are degraded.
- Histamine itself has no therapeutic action, only antagonists are used in clinical practice.

5.2.1 – Histamine Receptors

- There are 4 histamine receptors: H1, H2, H3, H4.
- H1 and H2 are the most relevant histamine receptors in clinical practice, but there is also one H3 antagonist occasionally used.

- Most commonly used antihistamines are H1 receptor antagonists, which are used for allergic reactions.



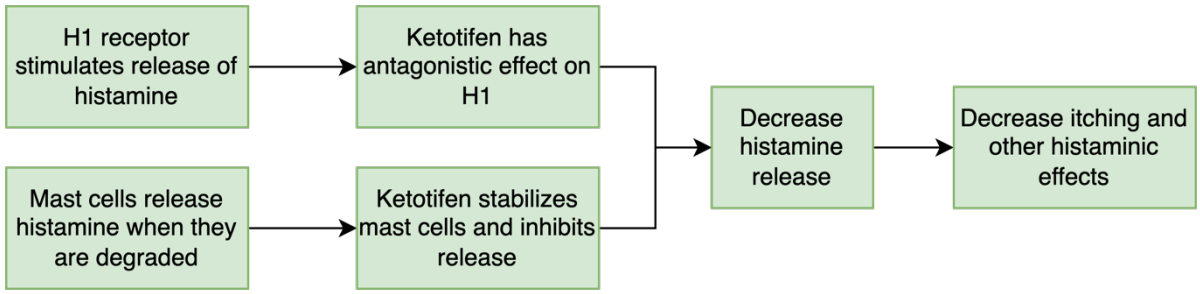
5.2.2 – Mast Cell Stabilizers

I. Mast cells

- Mast cells produce and release histamine in response to acute inflammation.
- Stabilization of mast cells will prevent degradation and will thereby decrease the release of histamine.

II. Ketotifen

- In addition to being a mast cell stabilizer, ketotifen is also a noncompetitive H1 receptor antagonist.
- Indicated for symptomatic treatment of allergic conjunctivitis by improving itching. Ketotifen is also used in allergic treatment, and is in rare cases used for asthma in children.



5.2.3 – H1 Receptor Antagonists

- H1 receptor antagonists are divided into first and second generation, which are differentiated by.
  1. Sedative effects
  2. Block of autonomic receptors
  3. Time of action
- These antagonists contain an alkylamine side chain that competes with histamine for the H1 receptor.
- The antiallergic effectivity of the drug is the same in both generations. Second generation has little or no sedative effect, and is therefore the drug class preferred for treatment of allergies.

	First-generation	Second-generation
Mechanism	Competitive receptor antagonists	
Effectivity	Equal	
Crosses BBB[1]	Yes	No
Sedative effect	Yes	Little or no
Antiemetic effect	Yes	No
Anticholinergic activity[2]	Yes	No
Clinical use	Allergy Hay fever Urticaria	
	Sedation Nausea and vomiting Motion sickness Vertigo	
Side effects	Sedation Atropine-like	Torsade's de pointes[3]
Drugs	**Diphenhydramine** **Chlorphenamine** **Cyclizine**	**Cetirizine** **Fexofenadine** **Loratadine**

[1] Drugs that are lipid soluble crosses the blood-brain-barrier and are able to interact with the central nervous system, they can therefore have sedative effects

[2] Drugs that have anticholinergic activity can cause atropine-like side effects. These side effects are covered in the chapter about PNS.

[3] QT interval prolongation in some second-generation antihistamines. These are now withdrawn from the market.

CLINICAL CORRELATION

Allergy

- Antihistamines are usually used to treat allergies.
- Zyrtec is the brand name of the second generation H1 receptor antagonists, cetirizine, which is commonly used.
- Helps relieve allergic symptoms such as itching, watery eyes, sneezing, runny nose, etc.

5.2.4 – H2 Receptor Antagonists

- Mostly related to gastric acid secretion.
- Will be covered in pharmacology exam 5.

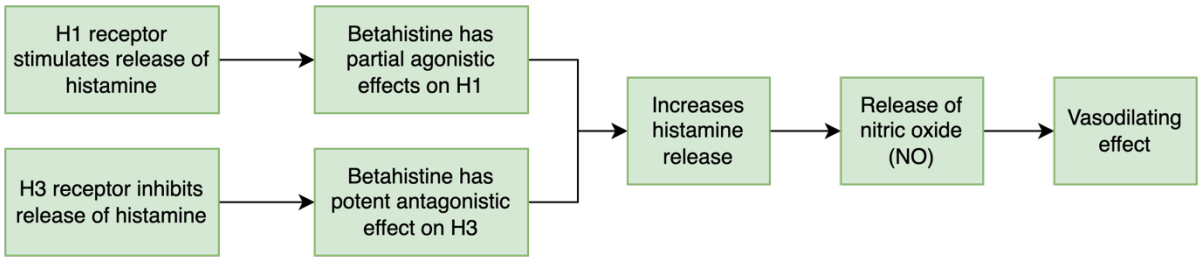
5.2.5 – H3 Receptor Antagonists

I. H3 receptor

- The H3 receptor is involved in histaminic neurotransmission in the central nervous system.
- Activation of this receptor results in inhibition of the release of histamine and other neurotransmitters.

II. Betahistine

- This is the only clinically active H3 antagonists, but is only used in a few countries due to no proven evidence of clinically effectiveness.
- Betahistine is also a partial H1 receptor agonist.
- The drug is used in symptomatic treatment of vertigo in Meniere's disease. Increased histamine results in vasodilation and thereby increased cerebral blood flow.

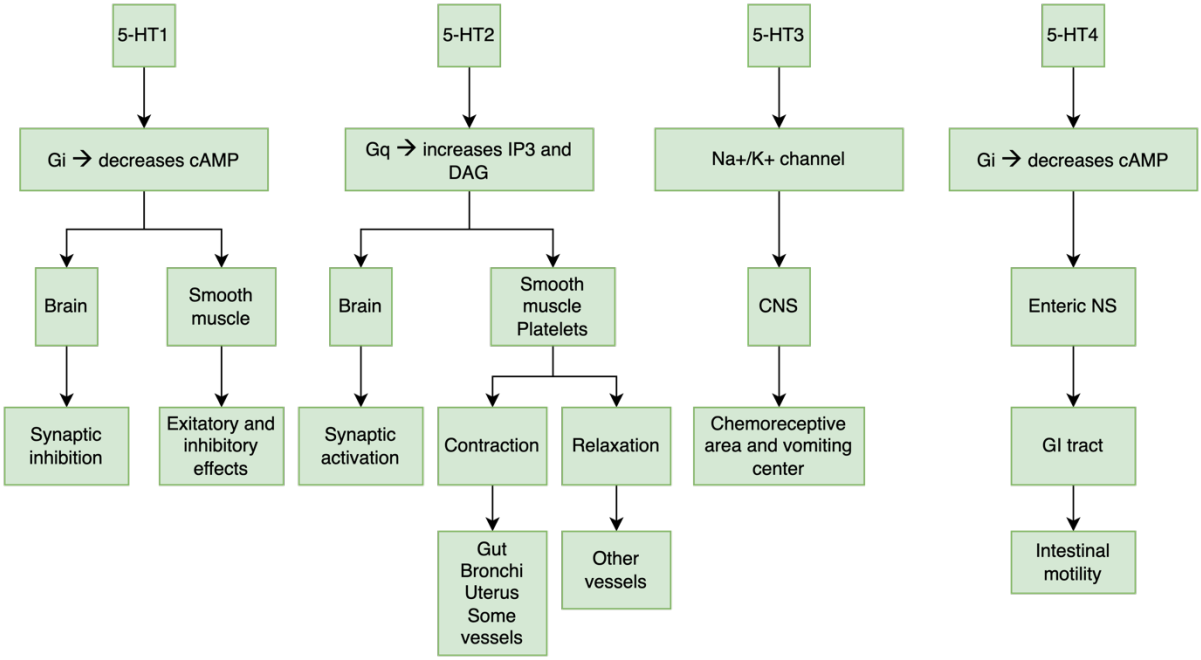


5.3 – Serotonin

- Serotonin is a neurotransmitter produced from tryptophan.
- It is a local hormone active in both the central nervous system and enteric nervous system.
- Serotonin plays a key role in many bodily functions such as mood and sleep.

5.3.1 – Serotonin Receptors

- Serotonin has 14 identified receptors. 5-$HT_{1D/1B}$, 5-HT_2, 5-HT_3, and 5-HT_4 are clinically relevant.
- Serotonin itself has no clinical use, but selective serotonergic agonists are proven to be effective.



5.3.2 – Serotonin Agonists

- These drugs carry the chance of developing serotonin syndrome. This syndrome will be covered in chapter 2.3.4.

SUFFIX

5-$HT_{1D/1B}$ agonists: -triptan

Drug class	Mechanism	Clinical use	Toxicity	Drugs
5-$HT_{1D/1B}$ agonists	Vasoconstriction of the cranial vessels, as well as inhibiting inflammatory neuropeptides	First line agents for migraine and cluster headache	Coronary vasospasms	**Triptans**
5-HT_{2C} agonists	The exact mechanism of this drug is not known, but it is thought to decrease appetite and promote fullness through receptors in the CNS	Obesity		**Lorcaserin**
5-HT_4 agonists	Increase intestinal motility	Gastroesophageal reflux disease, gastrointestinal hypomotility, and chronic constipation	QT prolongation[1]	**Cisapride**
			Increased risk of heart attack and stroke[1]	**Tegaserod**

[1] Both drugs are withdrawn from the market due to side effects. Currently there are no clinically used drugs, except for emergency cases.

CLINICAL CORRELATION

Migraine

- Triptans are the first-line agents to treat acute episodes of migraine.
- It is used to relieve the pain in migraine attacks, but cannot be used as prophylaxis to prevent the attack.
- Most commonly used is sumatriptan.

5.3.3 – Serotonin Antagonists

- Serotonin antagonists blocks the natural effects of serotonin.

SUFFIX

5-HT_3 antagonist: -setron

Drug class	Mechanism		Clinical use	Toxicity	Drugs
5-HT_2 antagonists	Competitive antagonists on the serotonin receptor in the brain and on smooth muscle	Blocks dopamine	Schizophrenia (antipsychotic)		**Clozapine**
		H1 antagonist	Allergic treatments and carcinoid tumors		**Cyproheptadine**
5-HT_3 antagonist	Blocks serotonergic effects on chemo reactive area and vomiting center by inhibiting Na/K channels		Antiemetic agent in chemotherapeutic cancer therapy, or nausea and vomiting from other causes	Diarrhea and headache	**Ondansetron**

CLINICAL CORRELATION

Antiemetic in chemotherapy

Ondansetron is commonly used to treat nausea and vomiting in patients that undergo cancer chemotherapy

5.3.4 – Serotonin Syndrome

- A syndrome that occurs when the serotonin level in the body is too high.
- Serotonin syndrome tends to occur within hours from drug consumption.
- Treatment is mainly symptomatic, but serotonin blockage can also be considered.
- In worst case, serotonin syndrome can be lethal.

CLINICAL CORRELATION

Serotonin syndrome

- Patient with depression treated with selective serotonin reuptake inhibitors (SSRI).
- Presents with hyperthermia, tremor, seizures, severe hypertension, mydriasis, GI symptoms, agitation, confusion, coma.
- SSRI increase the level of serotonin and is the most common drug to cause serotonin syndrome.

5.3.5 – Melatonin

- Melatonin is a serotonin derivative, and regulates the sleep cycle by inducing sleep.
- Melatonin is produced in response to darkness.

SUFFIX

Melatonin agonists: -melteon

I. Ramelteon

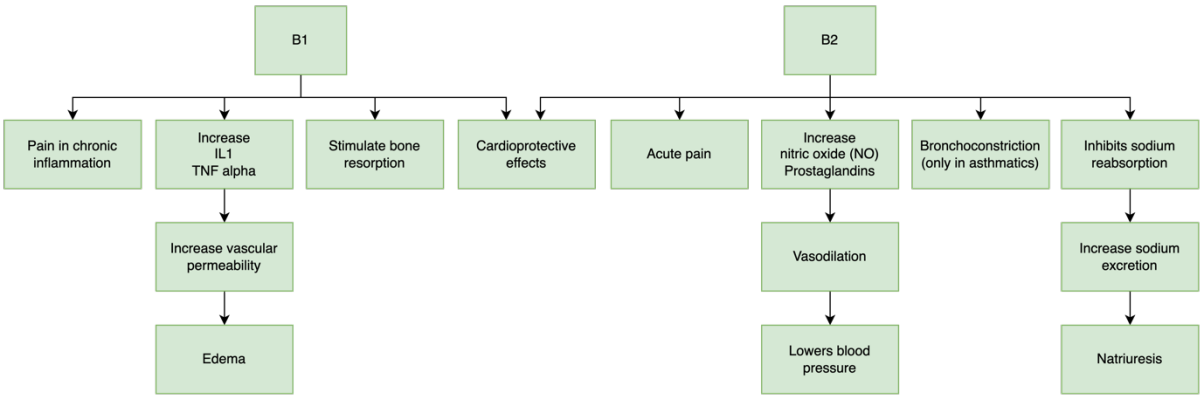
- Activates melatonin MT_1 and MT_2 receptors in the suprachiasmatic nucleus.
- Used to treat sleep disorders and jet lag symptoms.
- Toxicities include dizziness, fatigue and some endrocrine changes.
- Should not be used by pregnant women or nursing mothers.

5.4 – Bradykinin drugs

- A very potent vasodilator.
- Produced from kininogen by kallikreins.
- Bradykinin is degraded by angiotensin-converting enzyme (ACE).
- Is involved in inflammation and causes edema, vasodilation and pain.

5.4.1 – Receptors

- Acts through two receptors, B_1 and B_2.



5.4.2 – Drugs Inhibiting Bradykinin

	Mechanism	Clinical use
Ecallantide	Kallikrein inhibitor	Acute episodes of angioedema in patients with hereditary angioedema
Icatibant	B2 receptor antagonist	

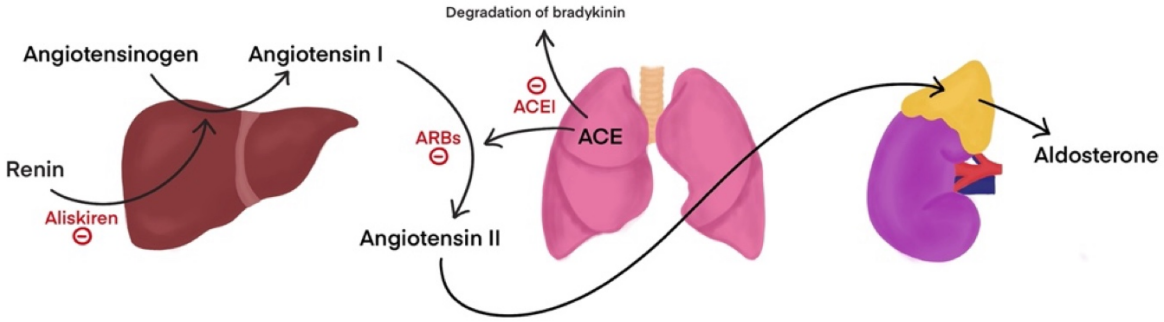
CLINICAL CORRELATION

Hereditary angioedema

- A hereditary disease characterized by repeated episodes of severe edema caused by a C1 inhibitor deficiency.
- Deficiency of C1 inhibitor results in activation of kallikrein and thereby increased concentration of bradykinin.
- Inhibitors of bradykinin production can treat hereditary angioedema by decreasing edema, vasodilation and pain.
- Triggers such as stress, trauma, surgery and certain drugs should also be avoided.

5.5 – Angiotensin Inhibitors

5.5.1 – Renin-Angiotensin-Aldosterone System (RAAS)



- Renin catalyzes the conversion from angiotensinogen to angiotensin I.
- Angiotensin-converting-enzyme (ACE) converts angiotensin I to angiotensin II, which is highly expressed in kidneys, heart and testes.
- Important functions of angiotensin II.
    1. Aldosterone release, which facilitates sodium and fluid retention in the collecting ducts. Sodium and fluid retention will result in potassium secretion.
    2. Sodium absorption in the proximal tubule.
    3. Vasoconstriction.
    4. Constricts efferent arterioles, and increases glomerular filtration rate (GFR).

5.5.2 – Renin Inhibitors

- Prevents release of renin. In difference to other angiotensin inhibitors, renin inhibitors also lower the levels of angiotensin I.

I. Aliskiren

- Direct renin inhibitor.
- Used in systemic hypertension.
- May lead to mild GI symptoms, headache, dizziness, fatigue and cough.
- Renin inhibitors are teratogenic.

5.5.3 – Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARB)

- ACE inhibitors and angiotensin receptor blockers inhibit conversion of angiotensin I to angiotensin II. This results in increase of both renin and angiotensin I.
- ACE inhibitors are the first line agent for chronic heart failure, but ARBs can be prescribed to patients who cannot tolerate ACE inhibitors.

SUFFIX

ACEI: -pril
ARBs: -sartan

	ACE inhibitors	ARB
Mechanism	Inhibits angiotensin-converting-enzyme (ACE)	Angiotensin receptor blockers
Clinical use	First line agents in treatment of chronic heart failure Hypertension	Hypertension Heart failure
Bradykinin increase[1]	Yes → cause cough	No
Side effects	Dry cough Hypotension[2]	No cough Hypotension[2]
Teratogenic	Yes	Yes

[1] Bradykinin is degraded by ACE, and inhibition of ACE will result in a spike in bradykinin. This spike can cause lung irritation and inflammation resulting in a dry cough very typical for ACEI

[2] A sudden drop in angiotensin II will result in vasodilation followed by hypotension, and can in some cases cause syncope

CLINICAL CORRELATION

Dry cough

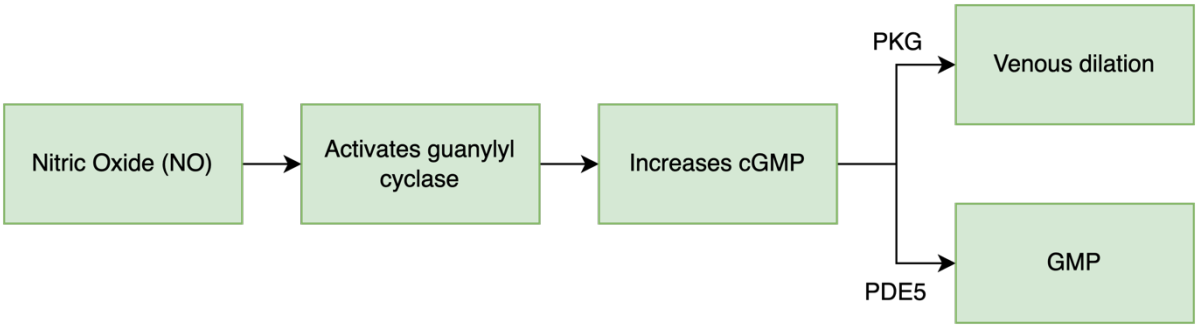
- Patient with hypertension treated with an ACE inhibitor start experiencing a dry cough.
- Cessation of the drug is required to stop the cough.
- Can change to an ARB, as they do not increase the bradykinin level and is less likely to cause a dry cough.

5.5.4 – Aldosterone Antagonists

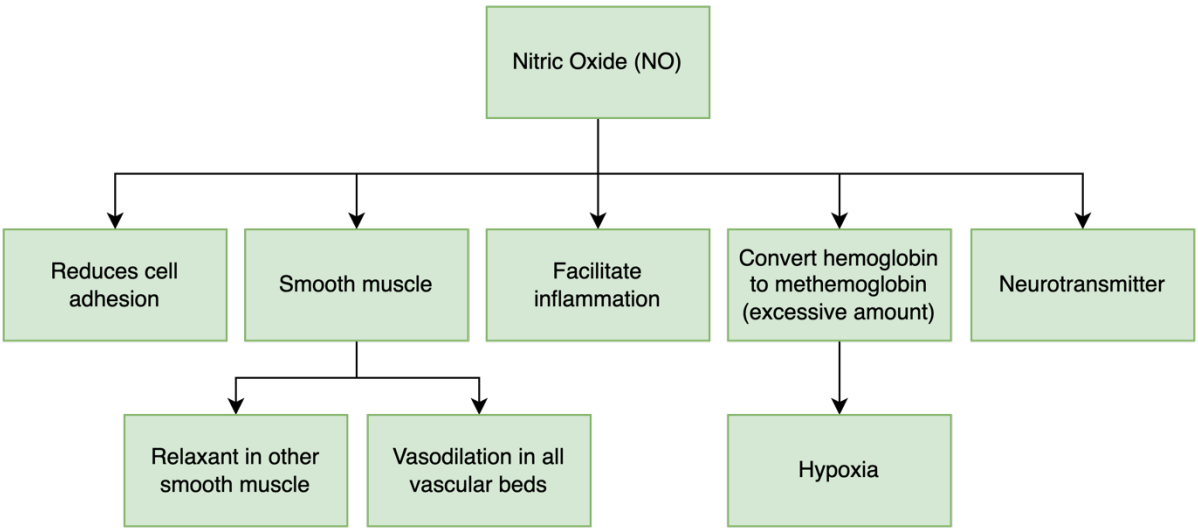
- Aldosterone antagonists inhibits retention of sodium and fluid in the collecting duct.
- Result in decreased sodium levels, decreased blood pressure, and increased potassium levels.
- These drugs will be covered in pharmacology exam 5 about diuretics.

5.6 – Nitric Oxide

- Nitric oxide is a very potent vasodilator. It is produced from arginine.



5.6.1 – Effects of Nitric Oxide



5.6.2 – Exogenous Nitric Oxide Donors

	Mechanism	Clinical use	Toxicity
Nitroglycerin	Exogenous nitric oxide (NO) donors → vasodilation[1]	Ischemic heart diseases, hypertensive emergencies, and acute pulmonary edema	Tachyphylaxis[3]
Molsidome			Do not cause tachyphylaxis
Sildenafil (Viagra)	Inhibits PDE5 and increases the vasodilatory effect of NO	Erectile dysfunction[2]	

[1]Improves the mismatch between oxygen supply and demand
[2]Treat erectile dysfunction by increasing blood flow to the erectile tissue
[3]Tachyphylaxis is an acute reduction in response of a drug

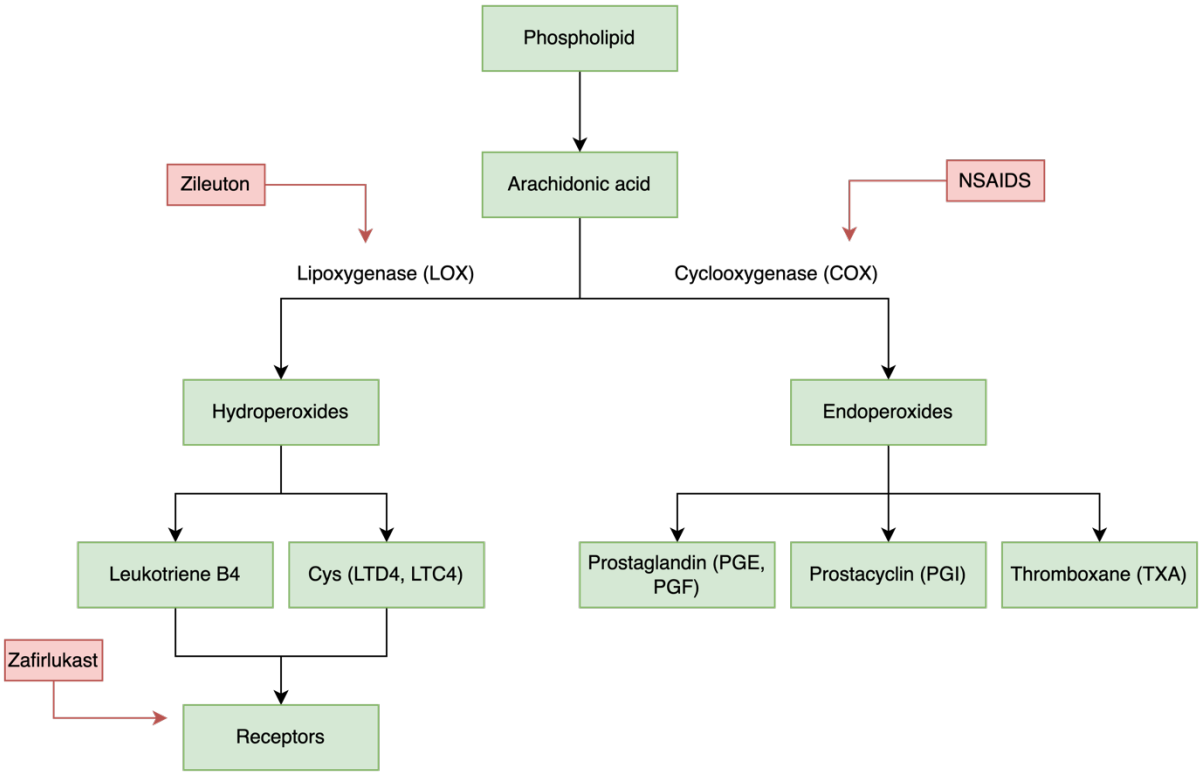
CLINICAL CORRELATION

Heart attack

- A patient presents with acute chest pain radiating to the left arm and jaw
- Morphine, oxygen, nitroglycerin and aspirin (MONA) is a regimen commonly used for suspected acute coronary syndrome
- Nitroglycerin is a vasodilator that improves blood flow to the heart and decrease the required work load

5.7 – Eicosanoids

- A class of molecules synthesized from arachidonic acid.
- Subgroups are leukotrienes, prostaglandins, prostacyclin, and thromboxane.



5.7.1 – Prostaglandin and Prostacyclin

- Synthesized from arachidonic acid by the enzyme cyclooxygenase (COX)

SUFFIX

Prostaglandins or prostacyclins: -prost-

	Mechanism	Clinical use	Toxicity	Drug
PGE1 analogs	Vasodilator Inhibits platelet aggregation Contracts uterine and intestinal smooth muscle	Maintain patent ductus arteriosus[1] Erectile dysfunction (second line)	Issues related to ductus arteriosus Erectile dysfunction	**Alprostadil**
		Prevent NSAID-induced peptic ulcers Facilitate labor or terminate pregnancy	Stomach pain, diarrhea, and termination of pregnancy	**Misoprostol**
PGE2 analogs	Promotes uterine contraction and softens the cervix	Facilitate labor or terminate pregnancy in the second trimester Maintain patent ductus arteriosus[1]	More GI side effects than other abortifacients, such as nausea, vomiting and diarrhea	**Diniprostone**
PGI2 analogs	Vasodilation and lowering of vascular resistance	Pulmonary hypertension	Flushing, headache, hypotension, nausea, and diarrhea	**Iloprost**
PGF2alpha analogs	Increases outflow of acquoes humor	Glaucoma	Brown pigmentation of the iris	**Latanoprost**

[1] Prostaglandins play a huge role in maintaining a patent ductus arteriosus. Is given to neonates with duct-dependent congenital heart defect that relies on a patent duct.

CLINICAL CORRELATION

NSAID-induced peptic ulcer

- A patient taking NSAIDs for rheumatoid arthritis starts experiencing a burning pain in the upper abdomen, as well as nausea and vomiting
- Endoscopy reveals a peptic ulcer in the stomach
- **Misopristol** taken together with NSAIDs can reduce the chance of patients developing an ulcer

CLINICAL CORRELATION

Transposition of the great arteries

- A congenital heart defect where the pulmonary artery and aorta are switched
- Resulting in deoxygenated blood being delivered to the body tissues
- Mixing of the circulations is required for survival
- PGE1 analogs are given to maintain a patent ductus arteriosus while waiting for surgical repair

5.7.2 – Leukotriene and Thromboxane

I. Thromboxane

- Drugs that inhibit COX will inhibit the formation of thromboxane (TXA). An example include aspirin.

II. Leukotrienes antagonists

- Results in bronchodilation and decreased mucus secretion in the airways.
- CysLT receptors antagonists are more commonly used than 5-lipooxygenase inhibitors.

SUFFIX

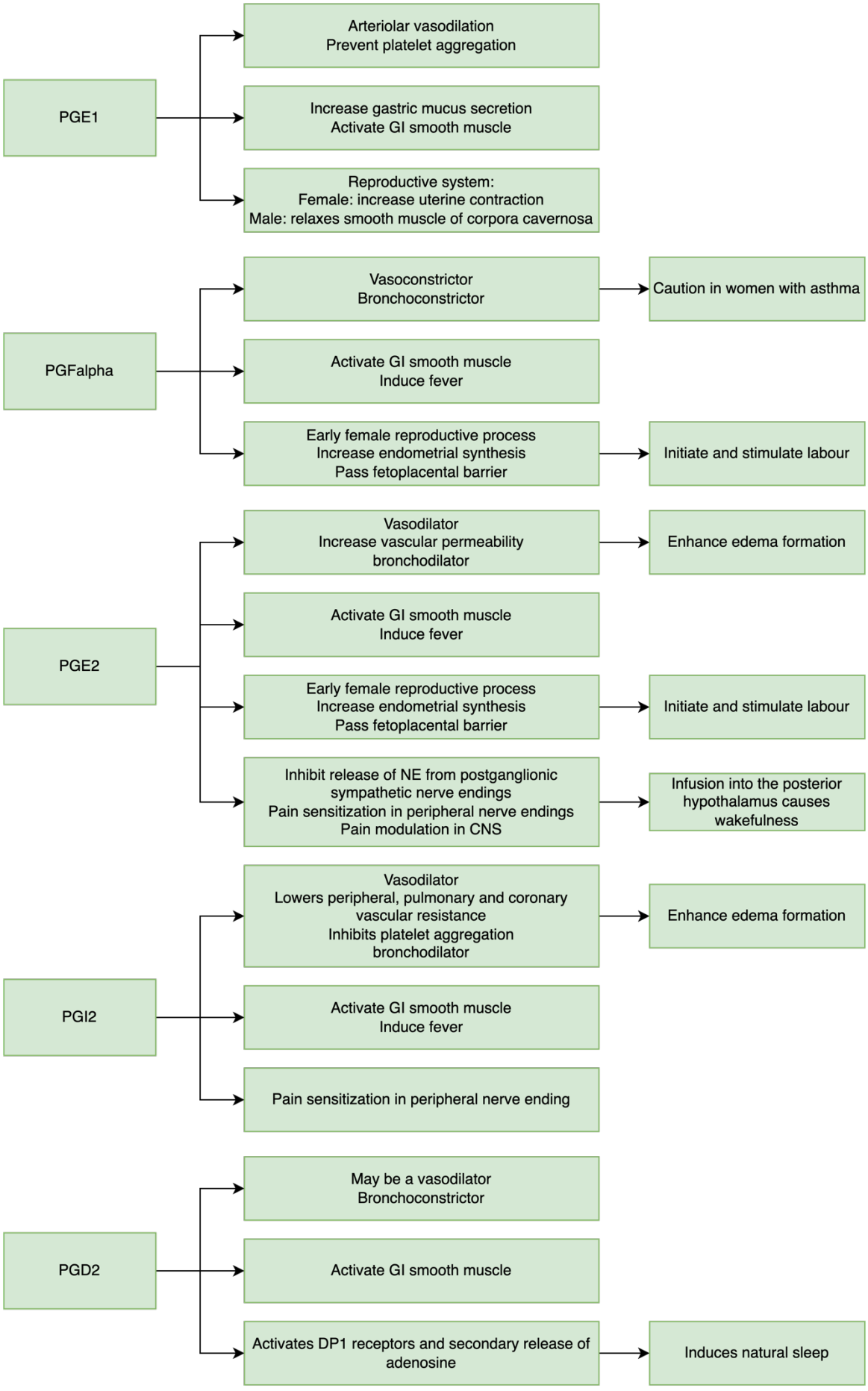
CysLTR antagonist: -lukast

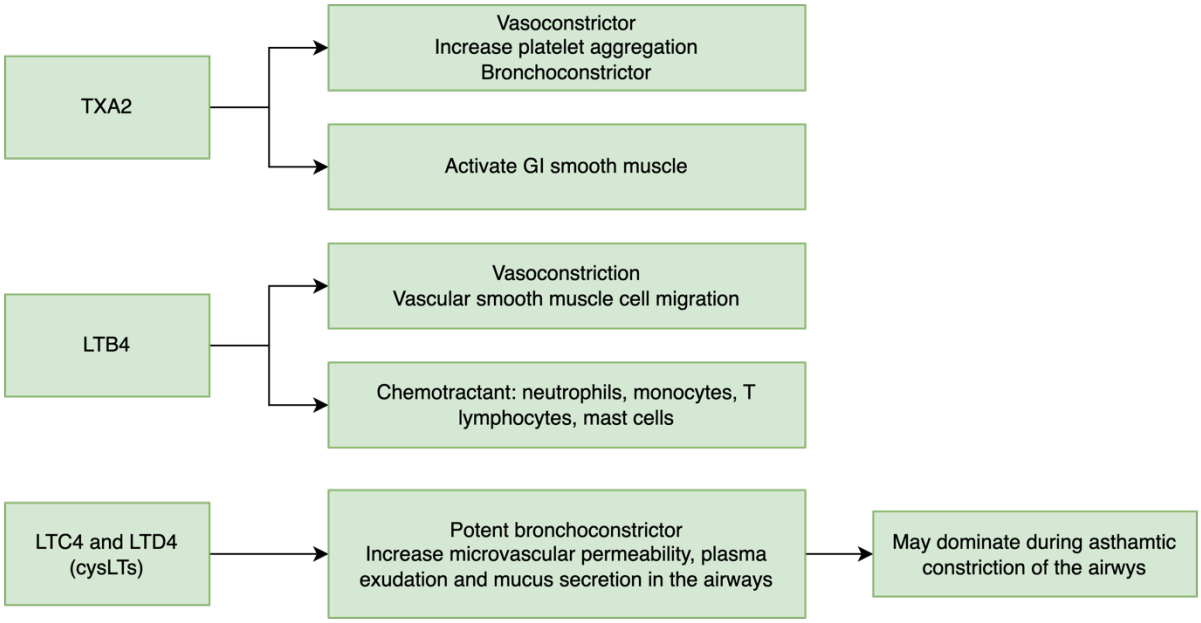
	Mechanism	Clinical use
Montelukast	CysLT receptor antagonist	Asthma
Zileuton	5-lipooxygenase inhibitor	

CLINICAL CORRELATION

Asthma

- A patient is taking inhaled steroids for asthma, but is still experiencing symptoms
- Montelukast can be prescribed to reduce inflammation in patient that do not improve symptoms with steroids
- The effect of Montelukast is delayed, so the drug should be used for long-term treatment of asthma and not in asthma attacks alone


PGE1
Arteriolar vasodilation
Prevent platelet aggregation
Increase gastric mucus secretion
Activate GI smooth muscle
Reproductive system:
Female: increase uterine contraction
Male: relaxes smooth muscle of corpora cavernosa
PGFalpha
Vasoconstrictor
Bronchoconstrictor
Caution in women with asthma
Activate GI smooth muscle
Induce fever
Early female reproductive process
Increase endometrial synthesis
Pass fetoplacental barrier
Initiate and stimulate labour
PGE2
Vasodilator
Increase vascular permeability
bronchodilator
Enhance edema formation
Activate GI smooth muscle
Induce fever
Early female reproductive process
Increase endometrial synthesis
Pass fetoplacental barrier
Initiate and stimulate labour
Inhibit release of NE from postganglionic sympathetic nerve endings
Pain sensitization in peripheral nerve endings
Pain modulation in CNS
Infusion into the posterior hypothalamus causes wakefulness
PGI2
Vasodilator
Lowers peripheral, pulmonary and coronary vascular resistance
Inhibits platelet aggregation
bronchodilator
Enhance edema formation
Activate GI smooth muscle
Induce fever
Pain sensitization in peripheral nerve ending
PGD2
May be a vasodilator
Bronchoconstrictor
Activate GI smooth muscle
Activates DP1 receptors and secondary release of adenosine
Induces natural sleep



5.8 – Endothelin

- Very potent vasoconstrictors with a long-lasting effect.
- There are three endothelin peptides
  1. Endothelin-1
  2. Endothelin-2
  3. Endothelin-3
- There are two receptors
  1. ET_A
  2. ET_B

I. Bosentan

- A classic endothelin-1 antagonist used for pulmonary hypertension. Endothelin-1 can cause vasoconstriction by binding to ET_A .
- Due to the risk of hepatotoxicity monthly liver tests are required. Other side effects include headache, pulmonary edema, nasal congestion, pharyngitis, and it has teratogenic potential.

CLINICAL CORRELATION

Pulmonary hypertension

- Bosentan is used to treat pulmonary arterial hypertension, but has severe hepatotoxic and teratogenic effects
- The benefit of the use of the drug should always outweigh the risk of adverse effects
- Due to high risk of adverse effects, pregnancy testing and AST/ALT levels should be performed monthly

5.9 - Test Yourself

1) What are the three main differences between first- and second-generation antihistamines?

_____

_____

2) What is the first-line treatment of migraine?

a) Propranolol
b) Sumatriptan
c) Cetirizine
d) Omaprazole

3) What is the drug ondansetron used for?

_____

_____

4) Which drug class is the most common cause of serotonin syndrome?

a) SSRI
b) Triptans
c) TCA
d) MOA-inhibitors

5) What is a specific side effect of ACE inhibitors? And why?

_____

_____

6) Which drugs can be used to maintain a patent ductus arteriosus?

a) NSAIDS
b) Beta-blockers
c) 1st generation antihistamines
d) Prostaglandin

7) What are leukotriene antagonists used for?

_____

_____

8) What is the first-line drug for erectile dysfunction?

a) Alprostadil

b) Sildenafil

c) Yohimibine

d) Clonidine

9) What is the mechanism of zafirlukast?

_____

_____

10) Which peptide is the cause of hereditary angioedema?

a) Bradykinin

b) Serotonin

c) Acetylcholine

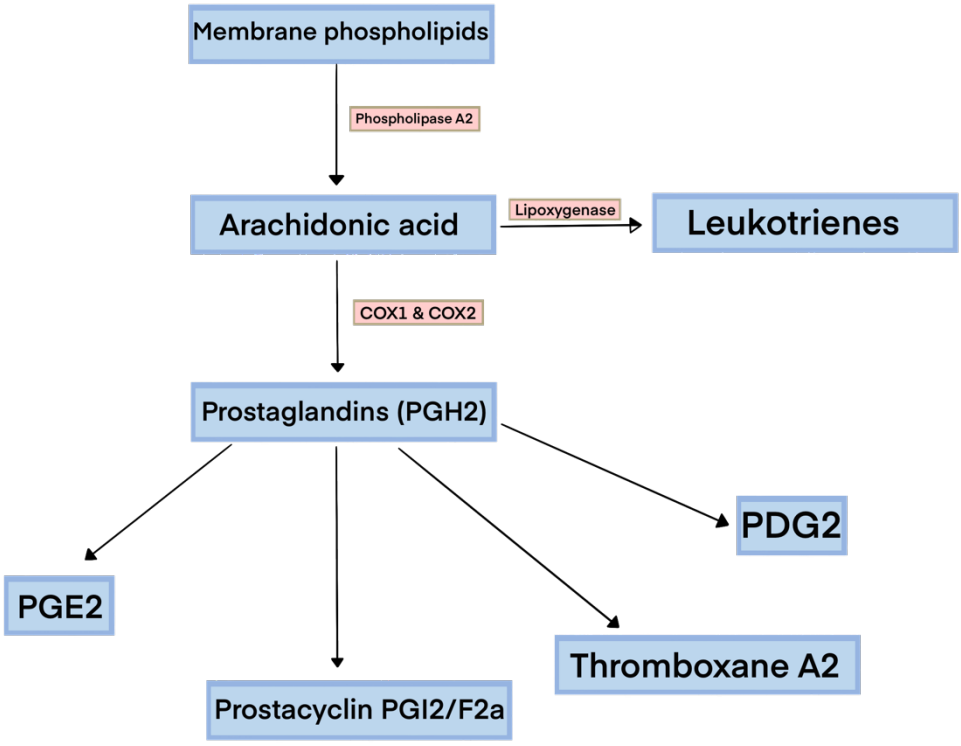
d) Histamine

11) Drag a line between the drug class and the suffix

Serotonin agonists	-Fil
Melatonin agonists	-Lukast
ACE inhibitors	-Prost-
ARBs	-Sartan
PDE-5 inhibitor	-Melteon
Prostaglandin and prostacyclin	-Zine
CysLTR antagonist	-Triptan
H1 antagonist	-Pril

6.1 – Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- NSAID's act by inhibiting the cyclooxygenase enzymes. This leads to decreased prostaglandin synthesis.
- NSAID's decrease COX activity primarily by competitive inhibition of the COX enzyme. However, aspirin is different because it covalently and irreversibly inhibits the COX enzyme.

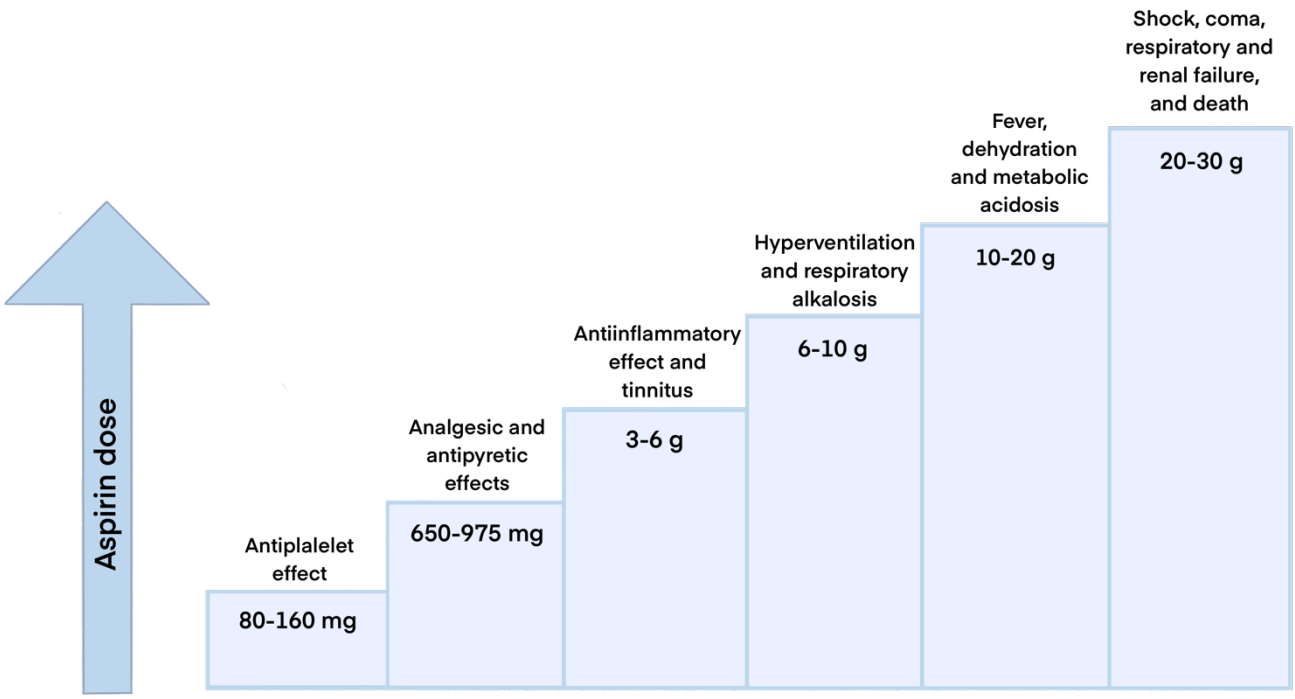


	Nonselective COX1 inhibitors	Selective COX2 inhibitors	Acetaminophen
Mechanism	Irreversible inhibition by binding to COX-1 enzyme.	Reversible inhibition by binding selectively to COX-2	
Action	Anti-inflammatory action by inhibition of COX-1. Analgesic and antipyretic actions by inhibiting PGE2 synthesis. Inhibit platelet aggregation by inhibition of TXA2.	Anti-inflammatory actions. Analgesic and antipyretic actions.	Inhibits prostaglandin synthesis in the CNS.
Clinical use	Osteoarthritis Gout Rheumatoid arthritis Headaches, myalgia, and dysmenorrhea. Fever Cardiovascular diseases	Rheumatoid arthritis Osteoarthritis Acute to moderate pain	Analgesic and antipyretic effects
Adverse reactions	Dyspepsia and GI bleeding Increased risk of bleeding. Kidney problems due to decreased renal blood flow.	Headache Dyspepsia GI upset	Substitute for the analgesic and antipyretic effects of NSAIDs for those with gastric complaints/risk. Children with viral infections.
Examples	**Aspirin** **Ibuprofen** **Ketoprofen** **Naproxen**	**Celecoxib** **Rofecoxib**	Hepatotoxicity

CLINICAL CORRELATION

Aspirin

Aspirin should be avoided in children, due to increased risk of Reye syndrome in children with viral illnesses.



6.2. – Drugs for gout

- Gout is an inflammatory arthritis that causes pain and swelling in your joints. It is caused by excessive production or underexcretion of uric acid.

6.2.1 – Drugs for Preventing Gout Attacks

- Uricosuric drugs, like probenecid, should not be combined with aspirin or other salicylates, because they interfere with the uricosuric action of these drugs.

	Mechanism	Action	Clinical use	Examples
Uricosuric drug	Competitively inhibits reabsorption of uric acid.	Increasing the excretion of uric acid in urine.	Prevent gout attacks	**Probenecid**
Xanthine oxidase inhibitor	Inhibits XO, the enzyme that converts hypoxanthine to xanthine, and xanthine to uric acid.	Decreases the production of uric acid.	Prevent gout attacks	**Allopurinol**
Catabolic enzyme preparation	Catalyzes the oxidation of uric acid to allantoin	Lowering serum uric acid	Refractory chronic gout	**Pegloticase**

6.2.2 – Drugs for Acute Gout Attacks

	Mechanism	Action	Clinical use
Indomethacin (NSAID)	Potent inhibitor of COX enzymes	Decreasing the production of prostaglandins and other autacoids	Treat gout attacks Closure of patent ductus arteriosus in neonates
Colchicine	Disruption of microtubules and inhibiting the motility of leukocytes	Blocking the ability to cause urate crystal-induced joint inflammation	Treat gout attacks

6.3 – Disease-Modifying Antirheumatic Drugs

- Drugs that slow the progression of joint erosions in patients with rheumatoid arthritis.

	Mechanism	Action	Clinical use	Side effects
Methotrexate	Inhibits human folate reductase. Inhibits lymphocyte proliferation.	Inhibits DNA synthesis. Suppress immune system.	Drug of choice for patients with rheumatoid arthritis.	GI, hematologic, hepatic, and pulmonary reactions. Liver enzyme elevation in up to 15%. Contraindicated in pregnancy.
Leflunomide	Inhibit dihydroorotate dehydrogenase.	Inhibit DNA replication and RNA synthesis in leukocytes and T-cells.	Second line in treatment of rheumatoid arthritis.	Diarrhea. Reversible alopecia. Teratogenic.
Hydroxy-chloroquine	The drug accumulates in lysosomes and inhibit lysosomal function.	Reduces chemotaxis and phagocytosis of immune cells.	Antimalarial drug. Used in rheumatoid arthritis.	GI disturbance. Blurred vision, scotomas, and nigh blindness.

6.4 – Tumor necrosis factor α (TNF-α) blocker

- TNF-α is a proinflammatory cytokine produced by macrophages and activated T-cells.
- Elevated levels of TNF-α is found in patients with rheumatoid arthritis, therefore TNF-α blocking agents are effective in treating this disease.
- All TNF-α blocking agents should be used with caution because they may cause serious infections and sepsis.

	Mechanism	Clinical use
Etanercept	Is a recombined protein that antagonizes TNF-α.	Rheumatoid arthritis if methotrexate is not adequate.
Infliximab	Chimeric human-murine monoclonal antibody that inactivates TNF-α	Chron's disease Rheumatoid arthritis
Adalimumab	Huma IgG1 monoclonal antibody specific for TNF-α.	Rheumatoid arthritis

6.5 – Test Yourself

1) Choose correct statement regarding nonsteroidal anti-inflammatory drugs

a) Act by inhibiting phospholipase A2

b) Act by inhibiting the cyclooxygenase enzymes

c) Act by inhibiting lipoxygenase

d) Increase the amount of prostaglandins

2) Why is aspirin contraindicated in children?

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_____

_____

3) What is the mechanism of action of probenecid?

a) Lowering serum uric acid

b) Increasing serum uric acid

c) Increasing the excretion of uric acid in urine.

d) Decreases the production of uric acid.

4) What is the mechanism of action of allopurinol?

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_____

_____

5) Which of these drugs disrupts microtubules and inhibits the motility of leukocytes?

a) Colchicine

b) Pegloticase

c) Probenecid

d) Leflunomide


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