

Chapter 6 -Pharmacology of Autocoids & their antagonists

Histamine and antihistaminics, 5-Hydroxytryptamine and its antagonists, Lipid derived autocoids and platelet activating factor. **4 hours;5-7 marks**

a) Histamines

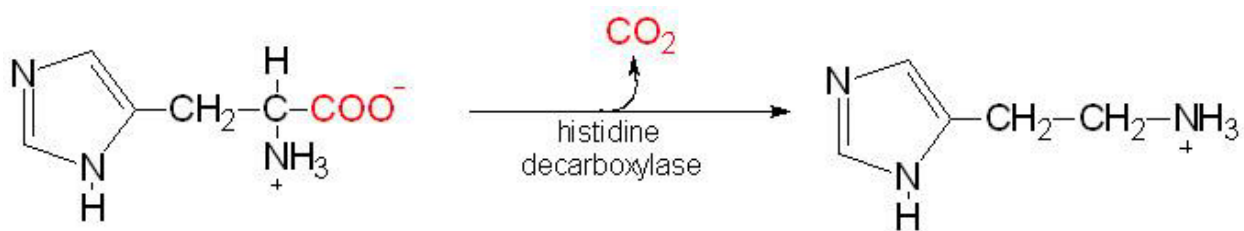
Autocoids- Autos= self, akos= remedy/healing. Autocoids are also called local hormones. Generally they act at the site of synthesis and release.

Classification of autocoids- 1.Amine autocoids- Histamine, 5 hydroxy tryptamine (5HT or serotonin).

2.Lipid derived autocoids- Prostaglandins, leukotrienes, platelet activating factors.(PAF).

3.Peptide autocoids- Plasma kinins (bradykinin, kallidin), angiotensin.

Histamine-It is present in the mast cells, basophils and platelets. It is present in high concentration in skin, lungs, gastric mucosa,and in the enterochromaffin cells in the stomach. It acts as neurotransmitter in the brain. Histamine is synthesized from the aminoacid L-histidine. The enzyme histidine decarboxylase catalyzes the conversion of L-histidine to histamine. In mast cells histamine (positively charged) is held by an acidic protein and heparin (-vely charged) within intracellular granules. When present in the cells it is inert but when released it becomes active and produces a number of biological actions. Release of histamine from mast cell occurs as a result of a. allergic reactions, b.chemical/drug induced- morphine, dTC, penicillins, and radio-contrast media. After release from the cells, histamine is rapidly degraded to methylation and oxidation and excreted in urine as metabolites (N-methyl imidazole acetic acid and imidazole acetic acid). It cannot cross BBB.



L-Histidine Histamine

Pharmacological actions of histamine-MOA- Histamine combines with specific receptors (H₁, H₂, and H₃) producing effects. All histaminic receptors are G-protein coupled receptors.

Histaminic receptors-

H₁- G_q- effector-PLC-> second messengers- IP₃ and DAG -> IP₃-> Increases Ca²⁺ concentration and DAG-> activation of PKC. The Ca²⁺ combines with calmodulin-> Ca²⁺-calmodulin activates MLCK-> phosphorylation of myosin light chain -> smooth muscle contraction.

Locations- Blood vessels, intestines, bronchi, uterus, nerve endings, and brain. Bronchial, intestinal smooth muscles-> contraction. Vascular endothelium -> vasodilatation through NO.

H2-Gs- effector-AC-> second messenger- cAMP-> activation of PKC.

Locations- Gastric parietal cells. Heart, uterus and brain. When histamine binds with H2 receptors present on the parietal cells-> stimulation of AC-> cAMP-> activation of PKC-> stimulation of the proton pump-> more H⁺ ions pumped out by these pumps, these H⁺ ions combines with Cl⁻ ions to form HCl.

H3-(Gi) Brain(auto receptor) These receptors are located on the central and peripheral nerves.

Actions of histamine-

1. Stimulate nerve ending- Itching and pain. (H1 receptor)

2. Smooth muscles- Contraction of smooth muscles of bronchii, intestine, uterus.(H1 receptor)

3. Exocrine secretions- Increase in salivary, lacrimal, bronchial, gastric juice secretions.

4. CVS- H1 and H2 receptors are involved.

a. Dilatation of the arterioles.

b. Increase in capillary permeability-edema.

c. **Triple response-** Intradermal injection of histamine (10-20µg) in man produces a characteristic effect called triple response. It consists of :

i) Development of a red spot within a minute at the site of injection, which is called 'flush'. The flush then gradually becomes a bluish discoloration. It is due to dilatation of capillaries and venules.

ii) Development of a bright red area called 'flare' which is irregular in outline and extending to 5cms beyond the flush. It is due to dilatation of arterioles produced by axon reflex.

iii) Development of localized oedema called 'wheal'. It is due to increased capillary permeability leading to exudation of plasma proteins and fluid from the capillaries into the extracellular spaces. The triple response is accompanied by itching.

d. Increase in heart rate and contraction.(H2 receptors)

e. CNS- Wakefulness, hypothermia, rise in BP, arousal, vomiting, nociception. (H1 & H2).

f. Gastric glands- Increase in gastric acid secretion.(H2).

Functions of endogenous histamine-

1. Regulates gastric acid secretion.

2. Plays a central role in immediate hypersensitivity responses.

3. Functions as a neurotransmitter in the brain.

Uses- Histamine has no therapeutic use. It is used in diagnostic tests.

1. Used to test acid secreting capacity of the stomach.

2. Used test B.P. rise due to release of catecholamines from the tumour of pheochromacytoma.

3. Used to test bronchial hyperactivity in asthmatics and allergic disorder.

4. To test the integrity of sensory nerves in leprosy (intradermal injection of histamine fails to elicit the flare in the affected region due to loss of axon reflex.)

4. Betahistine- (histamine analog) is used to control vertigo in Meniere's disease.

Antihistamines- (H1 blockers) are the drugs act by blocking the actions of histamine on H1 receptors.

Classification-

1. Highly sedative-Diphenhydramine, dimenhydrinate, promethazine, hydroxyzine.

2. Moderately sedative- Pheniramine, cypheptadine, meclizine, buclizine, cinnarazine.

3. Mild sedatives- Chlopheniramine, mepyramine, triprolidine, cyclizine, clemastine.

4. Non sedative antihistamines-Terfenadine, astemizole, loratidine, cetirizine,

Diphenhydramine- Diphenhydramine is used to treat sneezing, runny nose, watery eyes, hives(urticaria), skin rash, itching, and other cold or allergy symptoms. Diphenhydramine is also used to treat motion sickness, to induce sleep, and to treat certain symptoms of Parkinson's disease.

Dimenhhydrinate- (OTC drug used in motion sickness)- Motion sickness- Nausea, light headedness, giddiness caused by motion, especially by travelling in a vehicle. **Promethazine-** Promethazine is used to treat allergy symptoms such as itching, runny nose, sneezing, itchy or watery eyes, hives (urticaria), and itchy skin rashes. It also prevents motion sickness, and treats nausea and vomiting or pain after surgery. It is also used as a sedative or sleep aid.

Pheniramine (Pheniramine maleate-Avil) is an antihistamine with anticholinergic properties used to treat allergic conditions such as hay fever or urticaria. It has sedative effects also. Pheniramine is also used as eye drops to treat allergic conjunctivitis.

Pharmacological actions of antihistamines-

1. Vascular actions- Antihistamines block the histamine induced vasodilatation, increase in capillary permeability, edema and triple response. Act by blocking the H₁ receptors. No activation of PLC, and no formation of second messengers- IP₃ and DAG. This prevents the accumulation of calcium within the cells and causes anti-allergic effect.

2. Antiallergic actions- They relieve urticaria, itching and angioedema. Urticaria also known as hives is a kind of skin rash with red, raised, itchy bumps. Angioedema is the swelling (edema) of the dermis and subcutaneous tissue. Antihistamines also prevents the fall in BP bronchospasm. They also decrease the release of mediators from basophils and mast cells.

3. CNS- Depression-sedation, larger dose-> insomnia, restlessness, convulsions.

4. Anti- motion sickness action-Diphenhydramine, cyclizine, meclizine.

5. Antiemetic action-Promethazine, hydroxyzine.

6. Anti-parkinsonism action- Diphenhydramine, promethazine.

7. Anticholinergic action- Except non sedative antihistamines.

8. Alpha blocking action- Promethazine.

9. Local anesthetic action- Promethazine. Diphenhydramine.

10. 5HT antagonism- Cyproheptadine.

ADME-The classical H₁ antihistamines are well absorbed from oral and parenteral routes of administration. They are widely distributed in the body and enter the brain They get metabolized in the liver and the metabolites are excreted in urine.. The non sedative antihistamines penetrate brain poorly. Duration of action of most of the antihistamines 4-6 h, for some antihistamines-12-24 h.

ADRs- 1.Sedation, drowsiness, in coordination of movements, diplopia, blurred vision. 2. Anti-cholinergic effects- Dryness of mouth, urinary retention. 3. CVS-Hypotension, palpitation. 4. GIT- Anorexia, nausea, vomiting. 5. Miscellaneous- Teratogenic, contact dermatitis.

Uses- **1. Used in allergic conditions-** Urticaria, pruritus, food allergy, insect bite, hay fever (allergic rhinitis), drug allergy, and common cold. **2. Other uses-** a. To treat vertigo in Meniere's disease. b. Parkinsonism. c. Motion sickness. d. Antiemetic. e. Cough f. As sedative in children.

Marketed preparations.1.Diphenhydramine HCl tabs, syps.

2.Promethazine HCl suppositories, tablets, syrups.

3.Hydroxyzin HCl tabs,syps.

4. Chlorpheniramine tabs, inj, syps. 5. Cyproheptadine- tablet, syps.

6. Meclizine HCl tabs, 7. Mepyramine cream.

8. Cetirizine tabs, syrups.

H₂ blocker –Cimetidine, ranitidine, famotidine, nizatidine, roxatidine, loxatidine.

These are the agents which block the H₂ receptor mediated actions of histamine. They are mainly used in the treatment of peptic ulcer. They act by competitively blocking the H₂ receptors located on the gastric parietal cells of the gastric juice. This inhibits the formation of the HCl.

ADME-Well absorbed orally. These produce high first pass metabolism. Antacids decrease the absorption of these drugs.

ADRs-1. Cimetidine increases prolactin secretion- gynecomastia, decreased libido and impotence, (this is only with cimetidine), 2. Inhibition of cytochrome P-450 enzymes. This is with cimetidine only. This decreases the metabolism of other drugs. 3. Nausea, vomiting, diarrhea. 4. Reduces hepatic blood flow. 5. CNS- confusion, dizziness, restlessness. 6. Rarely allergic reactions, bone marrow depression. **Uses**- Duodenal ulcer, gastric ulcer, Zollinger-Ellison syndrome (increased secretion of gastrin), gastro-esophageal reflux disorder (GERD).

Preparations-Cimetidine 200, 400mg tabs, ranitidine 150, 300mg tab, 50mg inj.

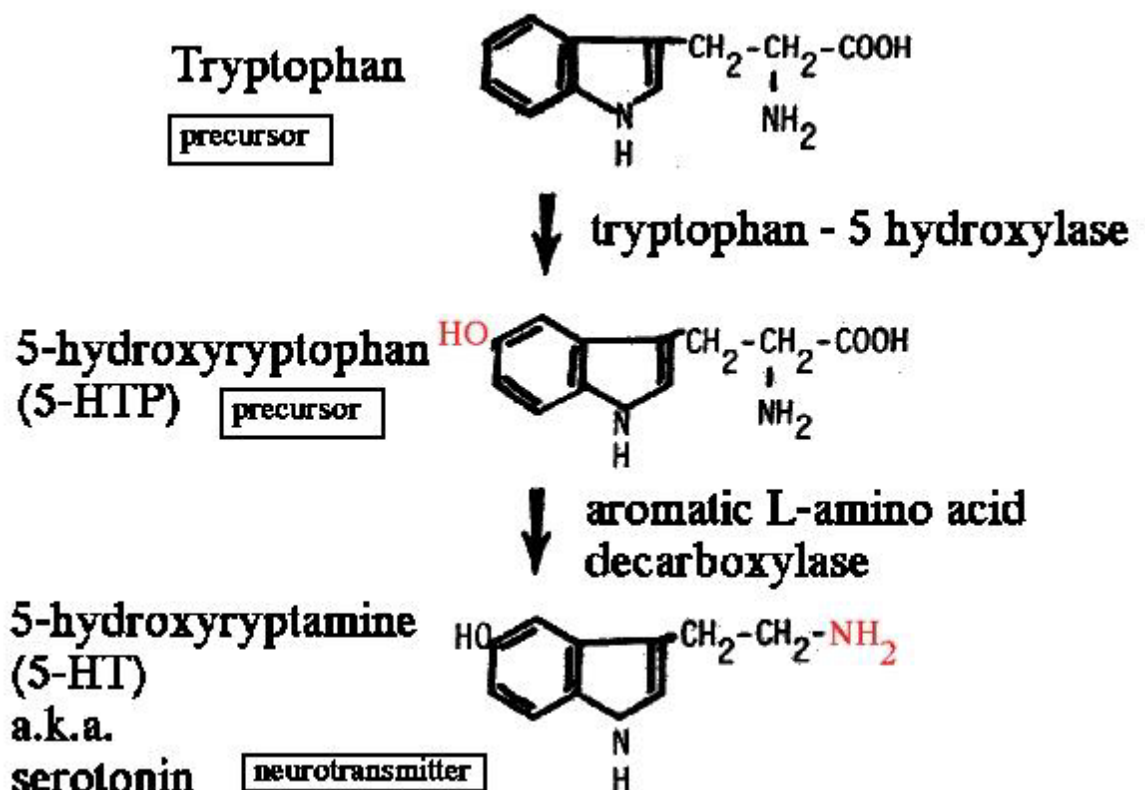
5-Hydroxy tryptamine (5HT, serotonin)

5HT is a monoamine neurotransmitter. Biochemically it is derived from tryptophan. It is popularly thought to be a contributor to feelings of well-being and happiness.

Synthesis and storage:

Tryptophan in diet is converted by tryptophan hydroxylase (rate-limiting enzyme) to 5-hydroxytryptophan which is converted by amino acid decarboxylase to 5-hydroxytryptamine (5-HT).

About 90% of 5-HT is stored in enterochromaffin cells of GIT, where it is used to regulate the intestinal movements. These cells contain tryptophan hydroxylase and can synthesize 5-HT. The remaining 10% are stored mainly in platelets and very small amount in CNS. In the CNS its function includes regulation of mood, appetite, and sleep. Serotonin also has some cognitive functions, including memory and learning. The platelets do not contain tryptophan hydroxylase and cannot synthesize 5-HT but obtain it by active uptake of 5-HT released from enterochromaffin cells into the blood. The 5HT is stored in the platelets.



Biosynthesis of 5HT

Fate of 5-HT: The majority of secreted 5-HT undergoes active reuptake into the serotonergic neurons. The remaining part of 5-HT is first metabolized (by oxidation) in the liver by monoamine oxidase (MAO) to the corresponding aldehyde. This is followed by oxidation by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid (5-HIAA) which is excreted in urine.

Serotonin (5-HT)-receptors:

There are 7 main types of 5HT receptors. Except 5-HT₃ all belongs to G protein coupled receptors.

5HT₁- Gi type, AC- decreased cAMP, inhibitory potential (IPSP).

5HT₂- Gq, PLC, IP₃, DAG, excitatory potential (EPSP).

5HT₃- Ligand gated Na⁺ and K⁺ cation channel, depolarization, excitatory.

5HT₄- Gs - AC, increase in cAMP, excitatory.

5HT₅- Gi- AC, decrease in cAMP, inhibitory.

5HT₆- Gs - AC, increase in cAMP, excitatory.

5HT₇- Gs - AC, increase in cAMP, excitatory.

5-HT₁-receptors: Sub types are 5HT_{1A}, 5HT_{1B}, 5HT_{1D}, 5HT_{1E} (all are located in the brain).

Actions of 5HT_{1A} – Antidepressant effect, hypothermia and hyperphagia (increased appetite).

Actions of 5HT_{1B} – Act as auto receptors, regulate the release of 5HT in the brain.

Actions of 5HT_{1D} - Act as auto receptors, regulate the release of 5HT in the brain.

Actions of 5HT_{1E} – Not clear.

5-HT₂-receptors: Sub types- 5HT_{2A}, 5HT_{2B} and 5HT_{2C}.

5HT_{2A}- These receptors are expressed on the vascular and visceral smooth muscle, platelets and cerebral neurons. The actions are vasoconstriction, intestinal, uterine and bronchial contraction, platelet aggregation and activation of cerebral neurons.

5HT_{2B}-These receptors are expressed on the gastric fundus. 5HT causes contraction of gastric fundus.

5HT_{2C}- These receptors are located in the endothelium of the blood vessels. 5HT causes vasodilatation through the formation of NO (EDRF).

5-HT₃-receptors: Ligand-gated ion channel receptors which increases intracellular Ca²⁺ / K⁺ concentration. They are present in GIT (increased peristalsis), peripheral nerve endings (pain and itching) and vomiting center of medulla (vomiting).

5-HT₄-receptors: In the brain –learning, memory, cognitive function. Also generates anxiety.

5HT₅ and 5HT₆ receptors: These are new receptors and actions are not clear.

Pharmacological actions of 5HT- **1.CVS-** Some blood vessels get constricted (direct effect) and some blood vessels get dilated (through the release of EDRF- NO). 5HT stimulates the heart directly and through the release of adrenaline.

2.Smooth muscles- 5HT causes contraction of the GIT smooth muscles- increased peristalsis and diarrhea. It also causes broncho-constriction.

3. Glands- 5HT inhibit the secretion of HCl and pepsinogen. But it increases mucous secretion. Hence it gives protection against peptic ulcer.

4. Nerve endings - 5HT causes sensitization of afferent nerve endings. This leads to pain and pricking sensation.

5. Respiration- Usual doses cause a brief stimulation of respiration, but larger doses leads to transient apnoea.

6. Platelets- 5HT produce weak platelet aggregator effect. 5HT also causes the alteration of the platelet shape.

7. CNS- 5 HT not crosses BBB and hence no central effects.

ADME- 5HT is inactivated on oral administration. It is absorbed on parenteral administration. The 5-HT is first metabolized (by oxidation) in the liver by monoamine oxidase (MAO) to the corresponding aldehyde. This is followed by oxidation by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid (5-HIAA) which is excreted in urine.

Physiological functions of 5-HT:

1. It acts as a neurotransmitter in the CNS (decreased brain serotonin results in anxiety, psychic depression) 2. It acts as a precursor for melatonin in the pineal gland.

3. It regulates GI motility.

4. It causes vasoconstriction and platelet aggregation in vessel injury (hemostasis).

5HT agonists and antagonists-

1.The anti-anxiety drug **buspirone** acts as a partial agonist of 5HT_{1A} receptor. **Partial agonists** bind to and activate a receptor, but are not able to elicit the maximum possible response that is produced by full agonists. A key property of partial agonists is that they display both agonistic and antagonistic effects. In the presence of a full agonist, a partial agonist will act as an antagonist, competing with the full agonist for the same receptor and thereby reducing the ability of the full agonist to produce its maximum effect.

Buspirone (trade name Buspar), is an anxiolyticpsychotropic drug of the azapirone chemical class. It is primarily used to treat generalized anxiety disorder (GAD).

(5HT₁- Gi type, AC- decreased cAMP, inhibitory potential (IPSP).

Actions of 5HT_{1A} – Antidepressant effect, hypothermia and hyperphagia (increased appetite))

2. **Sumatriptan** is an agonist on the presynaptic 5-HT_{1D} decreasing 5-HT release. It is a synthetic drug belonging to the triptan (tryptamine based drugs) class. It is used in treatment of acute attacks of migraine.

(Actions of 5HT_{1D} - Act as auto receptors, regulate the release of 5HT in the brain).

3. **Metoclopramide** is 5-HT₄ agonist used as prokinetic drug (stimulate tone and motility of GIT) in treatment of delayed gastric emptying and gastro esophageal reflux disorder (GERD). It is also used as antiemetic agent. (5HT₄- Gs - AC, increase in cAMP, excitatory.)

4. **Ondansetron** is 5-HT₃ antagonist used as antiemetic drugs for vomiting of cancer chemotherapy and postoperative vomiting. 5HT stimulate the 5HT₃ receptors are present on the cells of vomiting center of the medulla oblongata causing vomiting. Ondansetron prevents vomiting by blocking the 5HT₃ receptors. (5HT₃- Ligand gated Na⁺ and K⁺ cation channel, depolarization, excitatory).

5. **Cyproheptadine** is 5-HT₁ antagonist and antihistamine drug. It is used to treat allergic conditions and for the prophylaxis of migraine.

6. **Methysergide** is 5-HT antagonist used in prophylaxis of migraine and treatment of carcinoid syndrome (symptoms due to carcinoid tumors of GIT).

7. **Ketanserin** is a 5-HT_{2A} antagonist used in treatment of hypertension and peripheral vascular diseases. 5HT₂- Gq, PLC, IP₃, DAG, excitatory potential (EPSP). **5HT_{2A}**- These receptors are expressed on the vascular and visceral smooth muscle, platelets and cerebral neurons. The actions are vasoconstriction, intestinal, uterine and bronchial contraction, platelet aggregation and activation of cerebral neurons.

Lipid derived autocooids- Eicosanoids They are a group of unsaturated fatty acids composed of 20 carbon atoms and contain double bonds. Eg Prostaglandins, Leukotrienes, thromboxanes,

Biosynthesis of eicosanoids: They are synthesized from cell membrane phospholipids. The first step is separation of arachidonic acid from cell membrane phospholipids by the action of phospholipase A₂ which is stimulated during inflammation, allergy and cell injury.

Arachidonic acid is metabolized by one of two pathways to give different eicosanoids which are

I. Cyclooxygenase (COX) pathway- PGD₂, PGE₂, PGF₂, PGI₂, TXA₂

II. 5-Lipoxygenase pathway (LTA₄, LTB₄, LTC₄, LTD₄, LTE₄).

Biosynthesis of Eicosanoids (Leukotrienes)

Diacylglycerol & phospholipid (cell memb)
phospholipase C | Phospholipase A₂

↓
Arachidonic acid

↓ Lipoxygenase

HPETE (Hydroperoxyeicosatetraenoic acid)

↓

Leukotriene A₄ → LTB₄ (via H₂O)

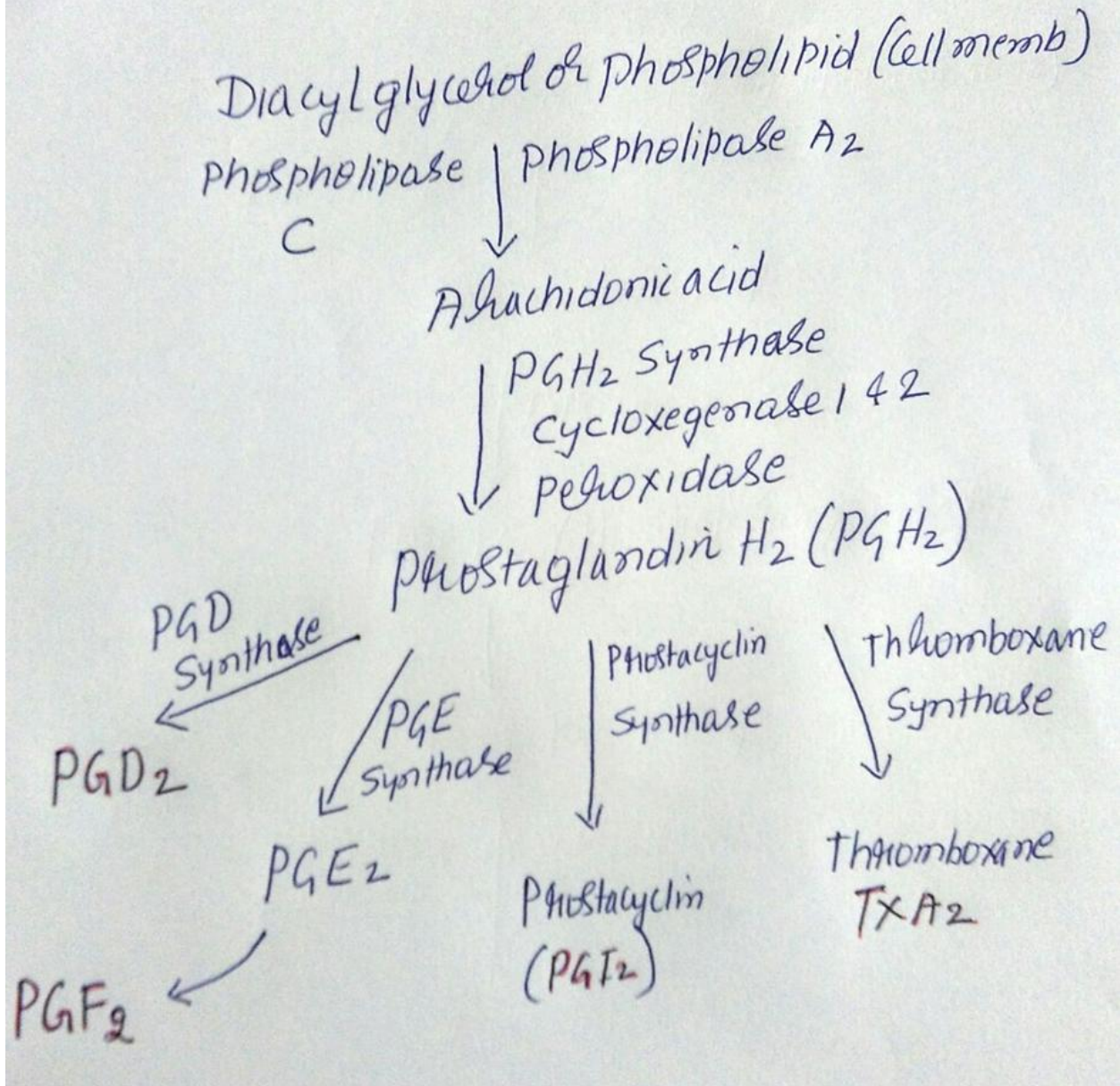
Glutathione | Glutathione-S-
transferase

↓
Leukotriene C₄

Glutamic Acid ↙ ↓
Leukotriene D₄

↓
Leukotriene E₄

Biosynthesis of Eicosanoids



Actions of prostaglandins, prostacyclins and thromboxanes

Prostaglandin receptors- There are currently ten known prostaglandin receptors on various cell types. These belong to G protein coupled receptors.

- 1. CVS-** PGD₂, PGE₂, and PGF₂ can increase the heart rate and force of heart contraction. TXA₂ and PGF₂ cause vasoconstriction. PGI₂ causes vasodilatation.
- 2. Platelets-** TXA₂ produced locally by platelets. It produces platelet aggregation effect.
- 3. Uterus-** PGE₂ and PGF₂ causes contraction of the uterus.

4. Bronchial muscle- PGD₂, PGF₂ and TXA₂ are the potent bronchoconstrictors. PGE₂ is a powerful bronchodilator.

5. GIT- PGE₂ reduces the acid secretion in the stomach, increases mucosal secretion and mucosal blood flow.

6. CNS- PGE₂ causes sedation, behavioral changes and rise in body temperature.

7. ANS- PGs may modulate the sympathetic neurotransmission.

8. Peripheral nerves- PGE₂ and PGI₂ increases sensitization of peripheral nerve endings.

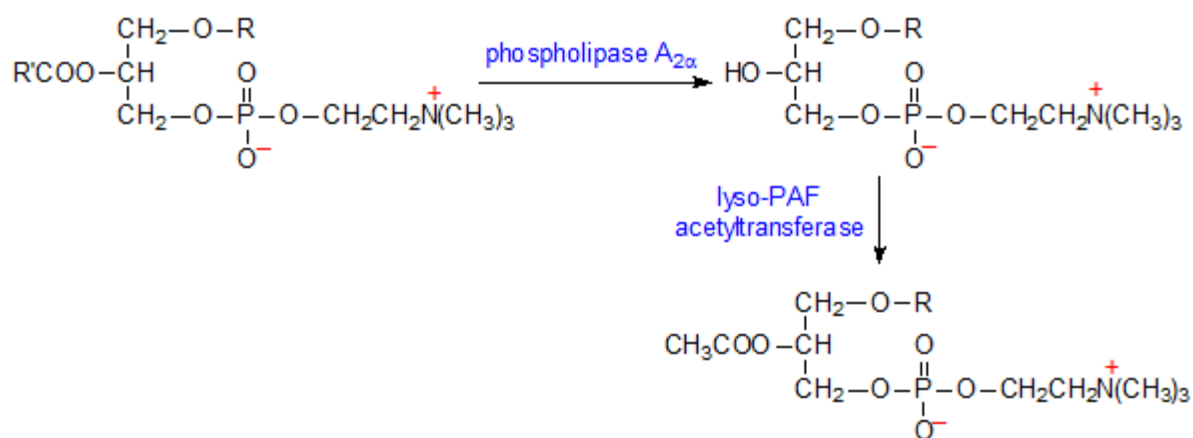
Therapeutic uses of prostaglandins:

1. PGF₂ (Dinoprost) and PGE₂ (Dinoprostone) are used as vaginal suppositories for therapeutic abortion (abortifacients) in early pregnancy and for induction of labor. 2. Misoprostol (synthetic analog of PGE₂) provides cytoprotective effect on gastric mucosa and is used in treatment of peptic ulcer and to prevent gastric ulceration during treatment with NSAIDs.

3. PGF₂ derivative (Latanoprost) decreases IOP by reducing aqueous humor synthesis and is used as eye drops for glaucoma.

Leukotrienes: Leukotrienes are a family of eicosanoid inflammatory mediators produced in leukocytes by the oxidation of arachidonic acid by lipoxygenase pathway. In inflammatory responses leukotrienes are also produced along with prostaglandins and histamine. LTC₄, LTD₄ and LTE₄ are cysteinyl leukotrienes due to the presence of amino acid cysteine in their structure. Through autocrine and paracrine signaling leukotrienes regulate immune responses. In asthma leukotrienes cause airflow obstruction, increased secretion of mucus, mucosal accumulation and bronchoconstriction. Both LTB₄ and the cysteinyl leukotrienes (LTC₄, LTD₄ and LTE₄) are partly degraded in local tissues and ultimately become inactive metabolites in the liver. Leukotrienes act on G-protein coupled receptors. Several leukotriene receptor antagonists such as montelukast and zafirlukast are used to treat asthma. **Platelet activating factor: (PAF).** It is a cell membrane derived phospholipids with wide range of biological activities. Chemically it is acetyl-glyceryl ether-phosphocholine.

Biosynthesis: It is synthesized from the precursor acylglycerophosphocholine present in the cell membrane by the action of the enzyme phospholipase-A₂. First lyso-PAF is formed and this is converted to PAF by the action of Lyso-PAF-acetyl transferase.



Degradation of PAF- It is degraded by the action of PAF acetylhydrolases.

PAF is produced by a variety of cells, but especially those involved in host defense, such as platelets, endothelial cells, neutrophils, monocytes, and macrophages. It is produced in larger quantities by inflammatory cells in response to specific stimuli.

Actions of PAF- PAF produces its effects through PAF receptors, which are expressed on the target cells. These receptors are G-protein coupled receptors.

CVS: It is a potent vasodilator. It causes the release of EDRF leading to fall of B.P. It increases capillary permeability leading to edema formation.

Respiratory tract effects: It has a strong role in inflammation. It can cause broncho-constriction and inflammation of airways. It can also produce edema of airways.

Haematological effects: It is a chemotactic (migration) factor for neutrophils, eosinophils and monocytes. It favors platelet aggregation.

GIT effects: It is ulcerogenic to gastric mucosa. It causes contraction of smooth muscles of GIT and increases gut motility.

Miscellaneous effects: It activates most inflammatory cells and plays important role in inflammation. It causes renal vasoconstriction and decreases urine output.

Anti PAF drugs- Clinical trials are going on to find its efficacy in atrial fibrillation and in allergy.