PHARMACOLOGY-II

UNIT 3 NOTES

AUTOCOIDS AND RELATED DRUGS

- Introduction and Classification
- Histamines, 5 HT and antagonists
- Prostaglandins, Thromboxanes and Leukotrienes
- Angiotensin, NSAIDs
- Anti Gout Drugs
- Antirheumatic Drugs

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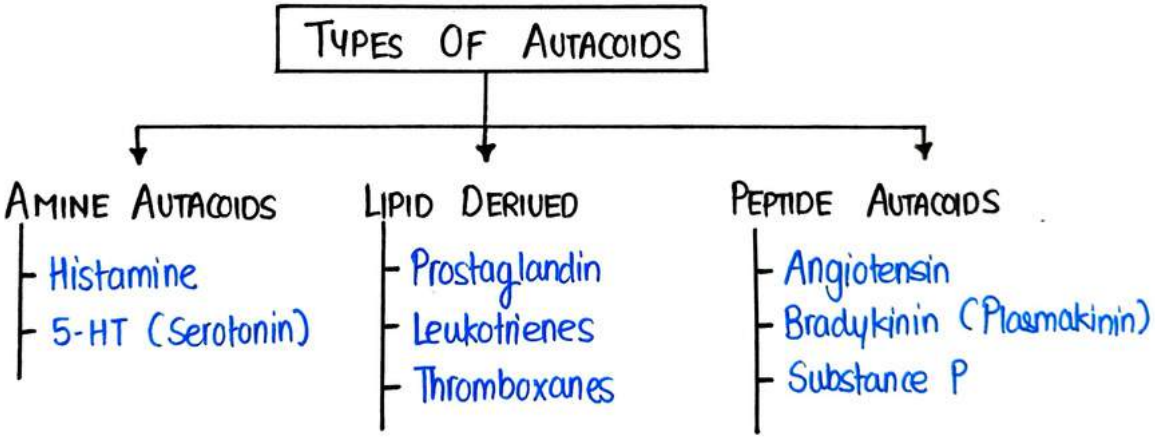
AUTACOIDS

- Autacoids are biologically active compounds that are produced by various tissues in the body and have a local effect on tissues where they are produced.
- They act as ~~signill~~ signalling molecules that regulate physiological processes, often having a short lived action.
- Autacoids are often produced in response to a stimulus, such as injury or inflammation, and they act on nearby tissues or cells to exert their effects, through receptors.



ANTIHISTAMINIC AGENTS

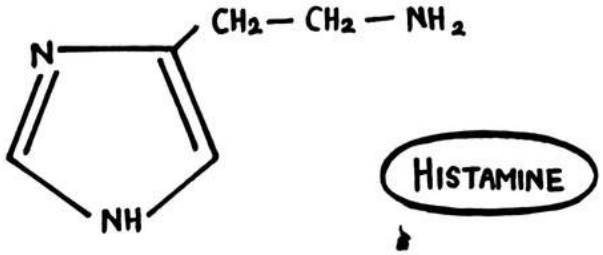
- Antihistaminic Agents, more commonly known as Antihistamines, are class of drugs used primarily to treat allergic reactions.
- They work by blocking the action of Histamine, a chemical in the body that is involved in allergic reactions.
- Histamine is released by immune system in response to allergens and is responsible for many of the symptoms associated with allergies such as itching, swelling and mucus production.

HISTAMINE

- Histamine is a type Amine Autacoid that plays several crucial roles in our body.
- It acts as a local hormone, act near the site of synthesis.
- It is stored in inactive form in granules of Mast Cells & Basophills and released upon activation.

CHEMICAL NATURE

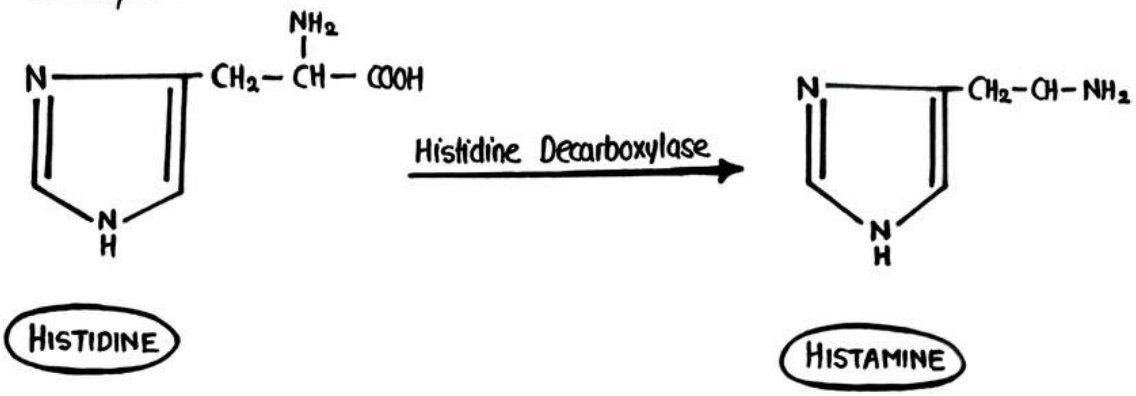
- Histamine is an organic nitrogenous compound with formula $C_5H_7N_3$
- It composed of an Imidazole Ring & Ethylamine side chain.



HISTAMINE

SYNTHESIS

Histamine is derived from amino acid Histidine through a process a process called Decarboxylation, catalyzed by enzyme Histidine Decarboxylase.

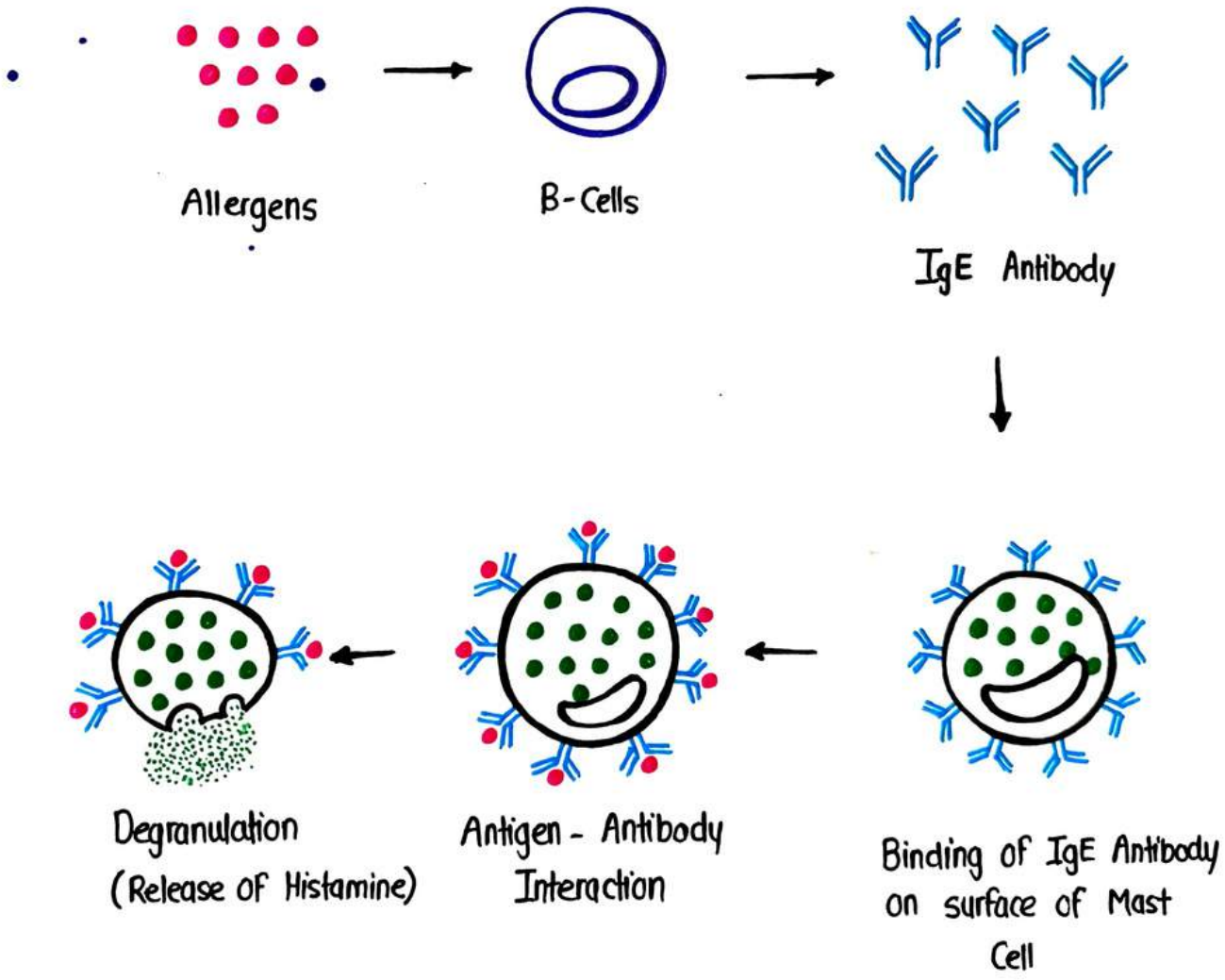


STORAGE

- Histamine is stored in the body primarily within Mast Cells and Basophills.
- It is stored in the granules of Mast Cells & Basophills.
- These granules are membrane bound vessicles that also contain other chemical mediators involved in inflammatory responses.
- It is stored in Mast cells in complex with 'Heparin' while in basophills stored in complex with 'Chondrotin'.
- Tissues that are rich in Histamines are skin, gastric and intestinal mucosa, lungs, liver, placenta & neurons of CNS.
- In stomach, Histamine is stored in Enterochromaffin - like cells (ECL Cells) that are found in gastric mucosa.
- In CNS, it is synthesized and released by specific neurons in brain as neurotransmitters.

Release Mechanism

- Histamine is released from Mast Cells & Basophills through a process called Degranulation.
- The process typically occurs in responses to an allergen or other immune triggers.
- In allergic reactions, Histamine is often released by triggers such as binding of allergen to IgE antibodies that are attached to the surface of Mast Cells & Basophills.



HISTAMINE RECEPTORS

	LOCATION	RECEPTOR	EFFECT
H_1	Throughout the body, specially in smooth muscles, vascular endothelial cells, Heart, CNS	Gi-Protein linked to intracellular Giq that activates Phospholipase C	Increased Vascular Permeability Bronchoconstriction, Increased Gut Motility
H_2	In more specific locations in the body mainly in gastric parietal cells, a low level can be found in vascular smooth muscles, Neutrophills, CNS, Heart, Uterus	Gi-Protein linked to intercellular Gis that stimulates Adenylcyclase and increases cAMP	Increase in Gastric Acid Secretion, Vasodilation
H_3	Found mostly in the CNS, with a high level in the thalamus, caudate nucleus & cortex, also a low level detected in small intestine, testis and prostate.	Gi-Protein possibly to intercellular Gi	Inhibit the synthesis and release of Histamine
H_4	Thymus Gland, Small intestine, Spleen Colon, Bone Marrow, Basophills	Unknown, Most likely also GPCR	Immune System Regulation

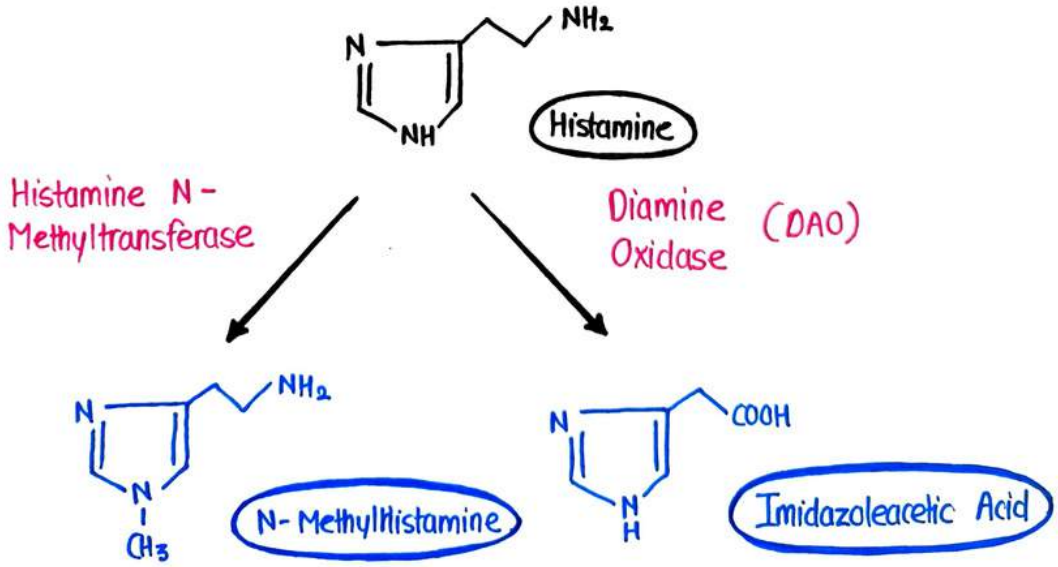
ACTION OF HISTAMINES

- As immune response it cause several symptoms such as itching, swelling & increased mucus production.
- Histamine cause blood vessels to dilate & become more permeable This results in increased blood flow to the affected area, which helps immune cells reach the site of infection or injury more efficiently
- It also leads to broncho constriction.
- In stomach it stimulates parietal cells to secrete gastric acid.
- In brain it acts as neurotransmitter and involved in regulating sleep-wake cycles, apetite & cognitive functions.

HISTAMINE METABOLISM

Histamine Metabolism occurs in the body through two major pathways:

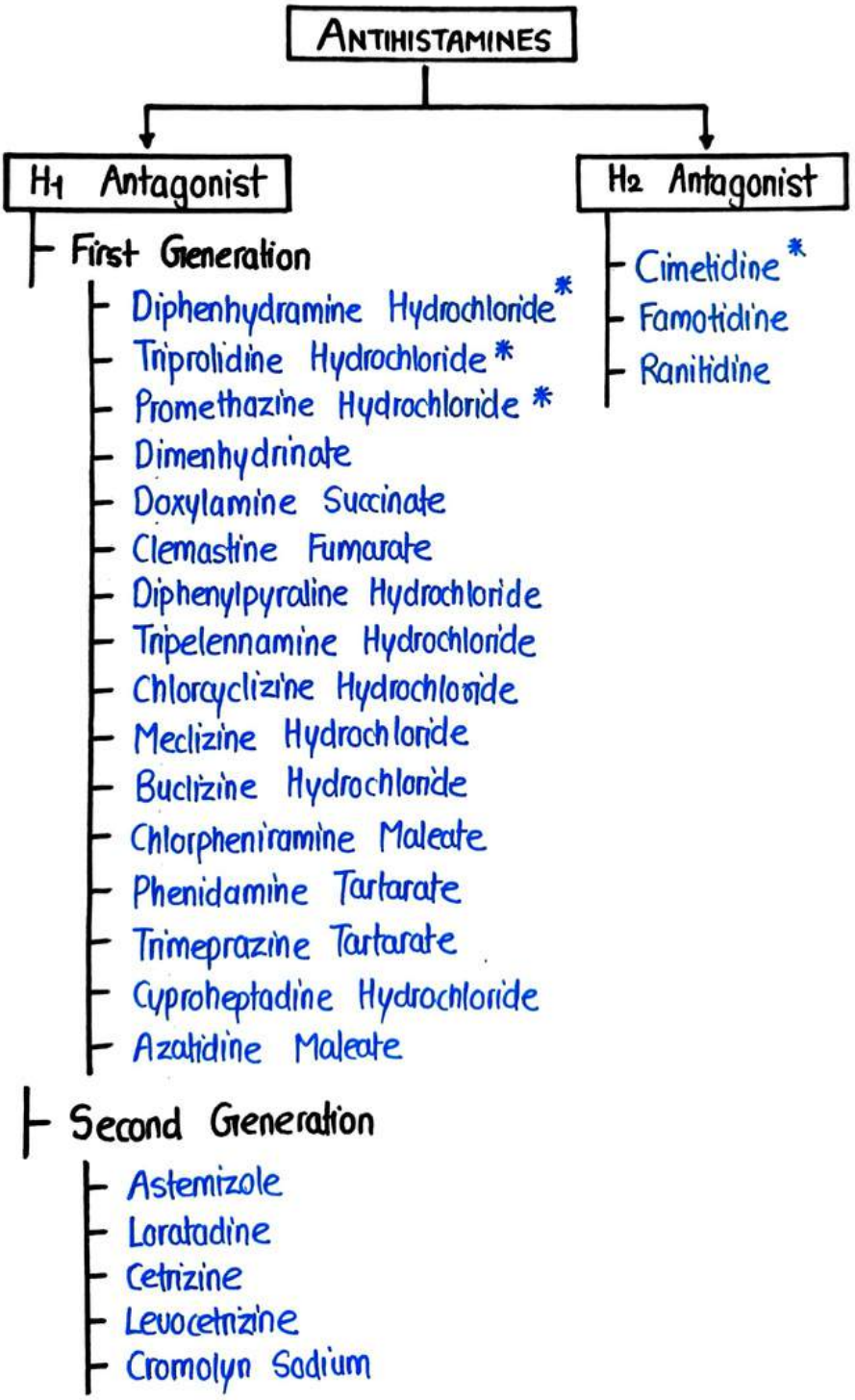
- Oxidation : By diamino Oxidase (DAO) to produce Imidazole Acetic Acid
- Methylation : By Histamine N-Methyltransferase to produce N-MethylHistamine.



Classification Of Antihistamines

Antihistaminic Drugs can be mainly classified into two types :

① H_1 Antagonist
② H_2 Antagonist



5-HT (SEROTONIN)

- Serotonin, also known by its name 5-Hydroxytryptamine (5-HT) is a coucial neurotransmitter & hormone involved in nemerous physiological functions.
- It is derived from amino acid Tryptophan and is primarily known for its role in mood regulation & overall mental well being.

LOCATIONS

- Central Nervous System
- Gastrointestinal Tract
- Platelets.

Functions

- Mood Regulation
- Sleep Regulation
- Cognition & Memory
- Sexual Desire
- Cardiovascular Health
- Wound Healing
- Apetite & Digestion

SEROTONIN RECEPTORS

- Serotonin receptors, also known as 5-HT Receptors that mediate the effects of serotonin, a key neurotransmitter & hormone.
- These receptors are widely distributed throughout the CNS & peripheral tissues, influencing numerous physiological functions:

Classification Of Serotonin Receptors

Serotonin receptors are classified into seven families (5-HT1 to 5HT-7) with several subtypes.

① 5-HT1 RECEPTORS

- Subtypes: 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F
- Mechanism: Inhibitory (reduce cellular activity by ↓ cAMP levels)
- Functions:
  - Regulate Mood & Anxiety
  - Mediate Vasoconstriction
  - Inhibit excessive neuronal firing
- Types: G-Protein Coupled Receptor

② 5-HT2 RECEPTORS

- Types: G-Protein Coupled Receptor
- Subtypes: 5-HT2A, 5-HT2B, 5-HT2C
- Mechanism: Excitatory (Increase intracellular Ca^{2+} & activates protein kinase C)
- Functions:
  - Regulate Mood, Perception and sleep
  - Plays role in cardiovascular function
-

③ 5-HT3 RECEPTORS

- Types : Ligand Gated Ion Channels
- Mechanism : Ionotropic (Mediates Ion Channel)
- Functions :
  - Regulate Nausea & Vomiting Reflexes.
  - Influence Pain perception & gut motility.

④ 5-HT4 RECEPTORS

- Types : G-Protein Coupled Receptors
- Mechanism : Excitatory (increase cAMP levels)
- Functions :
  - Regulate gastrointestinal motility
  - Modulate learning & memory process

⑤ 5-HT5 RECEPTORS

- Type : G-Protein Coupled Receptors
- Subtypes : 5-HT5A , 5-HT5B
- Mechanism : Likely inhibitory, but their functions are not well understood.
- Functions :
  - Mood Control

⑥ 5-HT6 Receptors

- Type : G- Protein Coupled Receptor
- Mechanism : Excitatory (increase cAMP levels)
- Function : • Regulate cognitive processes, such as learning and memory.

⑦ 5-HT7 Receptors

- Type : G- Protein Coupled Receptor
- Mechanism : Excitatory (increase cAMP levels)
- Function : Mood & Thermoregulation.

SEROTONIN ANTAGONIST

A serotonin antagonist is a drug or compound that blocks or reverses the action of serotonin at its receptors.

① CYPROHEPTADINE

- Cyproheptadine is a first gen antihistamine with additional antiserotonergic properties.
- It is commonly used for its ability to block histamine and serotonin activity, making it effective in treating allergies, migraines & serotonin syndrome.
- Common side effects include Drowsiness, sedation, dizziness, constipation, blurred vision etc.

② KETANSERIN

- ketanserin is a selective 5-HT2A receptor antagonist with additional effects on other receptors, including 5-HT2C & alpha-1 adrenergic receptors.
- Common side effects include dizziness, fatigue, Hypotension, nausea Edema etc.

③ RITANSERIN

- Ritanserin is a serotonin receptor antagonist that primarily targets 5-HT2A & 5-HT2C receptors.
- It is used in treatment of psychiatric conditions like depression, anxiety & schizophrenia.

④ Clozapine

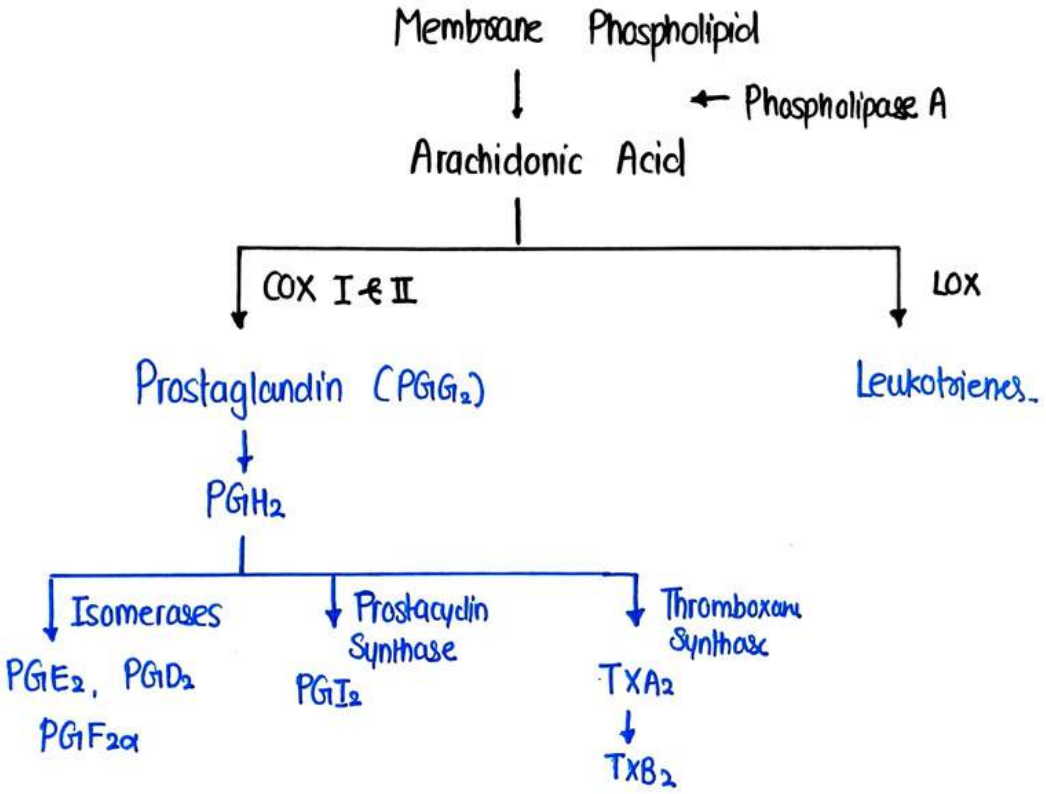
- It is 5-HT2A & 5-HT2C receptor antagonist.
- By Blocking 5-HT2C receptors it may influence mood & cognition,
- This mechanism might also contribute to weight gain & metabolic side effects.

⑤ RISPERIDONE

It is more effective in management of schizophrenia due to its additional D_4 receptor blocking activity apart from blockade of 5-HT2A & 5-HT2C receptors.

EICOSANOIDS

- Eicosanoids are 20-carbon unsaturated fatty acids derived mainly from arachidonic acid in cell membrane.
- The principle eicosanoids are Prostaglandin, Prostacyclin, Thromboxanes and Leukotrienes



① PROSTAGLANDINS

- Prostaglandins are group of lipid compounds that belong to eicosanoid family, derived from arachidonic acid.
- Since, first it was thought to originate in the prostate, it was called 'Prostaglandin' but later it was found to be produced in many tissues
- They are major lipid derived autacoids.

SYNTHESIS OF PROSTAGLANDINS

- Prostaglandin are synthesized from Arachidonic acid, a 20-Carbon polyunsaturated fatty acid
- Arachidonic acid is converted to prostaglandin G2 (PGG2) & Prostaglandin H2 (PGH2) by cox enzymes (COX-1 & COX-2)
- COX-1 : Constitutive, responsible for maintaining normal physiological functions like gastric protection
- COX-2 : Inducible, upregulated during inflammation & injury.

Physiological functions

Prostaglandins are not stored in cells but are synthesized on demand and act locally via specific GPCR receptors.

① Inflammatory Responses :
- PGE2 is a major mediator of pain, swelling & fever during inflammation
- Promotes vasodilation & increases vascular permeability to recruit immune cells to site of injury.

② Cardiovascular System :
- PGI2 (Prostacyclin) prevents thrombosis by inhibiting platelet aggregation & inducing vasodilation.

③ Reproductive System :
- PGF2α stimulates uterine contractions during menstruation & labour.

④ Gastrointestinal Protection :
- PGE2 stimulates mucus & bicarbonate secretion & inhibits gastric acid production, protecting stomach lining from damage.

⑤ Respiratory System :
- PGE2 : Bronchodilation
- PGF2α : Bronchoconstriction

⑦ Kidney Function :
- PGE2 & PGI2 regulate renal blood flow, GFR and sodium excretion.
- They play a critical role in maintaining kidney function during stress, such as hypovolemia.

⑧ CNS :
- PGD2 : involved in sleep regulation
- PGE2 : Modulates pain perception & thermoregulation.

② THROMBOXANE A2

Thromboxane A2 is a potent bioactive lipid involved in platelet aggregation and vasoconstriction, playing a key role in process of blood clot formation.

Synthesis

- TXA2 is produced from arachidonic acid through cox pathway.
- The enzyme thromboxane synthase converts prostaglandin H2 into TXA2.
- The synthesis typically occurs in platelets, crucial for clotting.

Function

- Thromboxane A2 promotes aggregation of platelets, which is an essential step in forming a blood clot at site of vascular injury.
- TXA2 causes blood vessels to constrict, help reducing blood flow and facilitate clot formation at injury site.
- It contributes to inflammatory responses by affecting various cells, including endothelial cells, smooth muscle cells & immune cells.

③ LEUKOTRIENES

- Leukotrienes are bioactive lipid mediators derived from arachidonic acid, a polyunsaturated fatty acid present in cell membranes.
- They belong to eicosanoid family & play vital roles in inflammatory & immune responses, particularly in conditions like Asthama, Allergies & chronic inflammation.

Synthesis Pathway

Leukotrienes are synthesized via lipooxygenase pathway from arachidonic acid in certain immune cells, such as mast cells, eosinophills, neutrophills, macrophages and basophills.

Types

It is categorized into two categories:

① Cysteinyl Leukotrienes:
- LTC4, LTD4, LTE4
- Induce bronchoconstriction
- Increase vascular permeability.
- Contribute to mucus production.

② Non- Cysteinyl Leukotrienes:
- LTB4
- Act as a potent chemoattractant
- Promotes inflammation by recruiting immune cells to injury sites.

PEPTIDE AUTACOIDS

- Peptide Autacoids are biologically active peptides that act as local mediators to regulate various physiological & pathological processes.
- They are of mainly 3 types :

① Bradykinin
② Angiotensin
③ Substance P

① BRADYKININ

Bradykinin is a nanopeptide (Composed of 9 amino acids) that functions as a powerful vasodilator & mediator of inflammation, pain & other physiological processes.

Synthesis & Metabolism

- Bradykinin is derived from kininogens (either HMW or LMW) which are plasma proteins by the reaction of kallikrein enzyme
- It has a short half life & rapidly degraded by ACE, Aminopeptidas P or Neutral Endopeptidase.

Receptors

- B2 Receptors :
  - It is expressed in most tissues.
  - Mediates most of bradykinin's physiological effects under normal condition.
- B1 Receptors :
  - Induced during inflammation, injury or infection.
  - Contributes to prolong inflammatory & pain response.

Functions

- Vasodilation by stimulating the release of Nitric Oxide, Prostacyclin and Endothelium-derived hyperpolarizing factors.
- Increases vascular permeability during inflammation.
- Pain Sensation
- Smooth Muscle Contractions (Non-vascular).
- Increases Renal blood flow.

② ANGIOTENSIN

- Angiotensin is a key peptide hormone involved in regulation of blood pressure and fluid balance.
- It is a part of Renin- Angiotensin- Aldosterone System (RAAS), which plays a critical role in maintaining blood pressure, electrolyte balance and overall fluid homeostasis.

KEY COMPONENTS & FUNCTION

- Angiotensinogen : It is the precursor of Angiotensin produced by liver.
- Renin : It is the enzyme released by kidneys when blood pressure drops that converts Angiotensinogen into Angiotensin I.
- Angiotensin- Converting Enzyme : Angiotensin I is then converted to Angiotensin II by ACE enzyme.
- Angiotensin II : It is the active form of Angiotensin & has several effects on the body.
  - Vasoconstriction.
  - Aldosterone Release.
  - ADH Hormone release.
  - Thirst Stimulation

ANGIOTENSIN RECEPTORS

- AT1 Receptors : Mediates most of the classical effects of Angiotensin II, including vasoconstriction, aldosterone release & sodium retention.
- AT2 Receptors : Have opposing effects to AT1 receptors. promoting vasodilation, anti inflammatory responses & tissue repair.

③ SUBSTANCE P

- Substance P is a neuropeptide that functions as a key mediator in transmission of pain signals & various inflammatory responses
- It belongs to tachykinin family of neuropeptides.

SOURCES & DISTRIBUTION

It is widely distributed in both CNS & PNS.
Found mainly in

- Sensory Neurons
- Enteric Nervous System.
- Immun cells.

MOA

Substance P exerts its biological effects primarily by binding to Neurokinin-1 receptors, a G-Protein Coupled Receptor.

Functions

- It is a key neurotransmitter involved in transmission of pain signals from periphery to CNS.
- It also triggers the release of inflammatory mediators like Histamine & Prostaglandins from mast cells & other immune cells.
- It also stimulate release of Nitric Oxide.
- Enhances activity of immune cells.
- It is also involved in mood regulation & stress response.

NSAIDs

- NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are a class of medications widely used to reduce inflammation, relieve pain and lower fever.
- They work by inhibiting enzymes called Cyclooxygenases (COX-1 & COX-2), which are involved in production of Prostaglandins - substances that contribute to inflammation, pain and fever.
- They are less potent than Narcotic Analgesic.

CLASSIFICATION OF NSAIDs

NSAIDs can be classified as follows:

① NON SELECTIVE COX INHIBITORS

- Salicylates : • Aspirin
- Propionic Acid Derivative : • Ibuprofen
  • Naproxen
  • ketoprofen
  • Flurbiprofen
- Fenamate : • Mephenamic Acid
- Enolic Acid Derivatives : • Piroxicam
  • Tenoxicam
- Acetic Acid Derivatives : • ketorolac
  • Indomethacin
  • Nabumetone
- Pyrazolone Derivatives : • Phenylbutazone
  • Oxyphenbutazone

② Preferential COX-2 Inhibitors

- Nimesulide
- Diclofenac
- Aceclofenac
- Meloxicam
- Etodolac

③ Selective COX 2 Inhibitors

- Celecoxib
- Etoricoxib
- Parecoxib

④ Analgesic Antipyretic With Poor Antiinflammatory Action

- Paraaminophenol Derivative : Paracetamol
- Pyrazolone Derivative : Metamizol , Propiphenazone
- Benzoxazocine Derivative : Nefopam

① NON SELECTIVE COX INHIBITORS

@ Salicylates

- Salicylates are a class of medications derived from Salicylic Acid that possess anti-inflammatory, analgesic & antipyretic properties.
- Aspirin is the prototype drug in salicylates.

ASPIRIN

- Aspirin is the prototype drug in salicylates.
- Its effects are primarily mediated through inhibition of COX enzymes.

MOA

Aspirin irreversibly inhibits COX-1 & COX2 enzymes which are involved in the conversion of arachidonic acid into Prostaglandin & Thromboxanes.

PHARMACOKINETICS

- Absorption: It is rapidly absorbed after oral administration.
- Distribution: It is widely distributed in tissues and binds to plasma proteins.
- Metabolism: Aspirin is hydrolyzed to salicylic acid by esterases in liver, blood & tissues where it is further metabolized in liver via conjugation.
- Excretion: It is excreted primarily through kidneys.

Therapeutic Uses

- Pain & Fever
- Inflammatory Conditions.
- Cardiovascular Protection.

Adverse Effects

- Ulcers
- Bleeding
- Dizziness
- Metabolic Acidosis

② PROPIONIC ACID DERIVATIVES

- Propionic Acid derivatives are subclass of Non- Selective Cox Inhibitors that are widely used for their analgesic, anti- inflammatory & antipyretic properties.
- These drugs are structurally based on proplonic acid & work primarily by inhibiting cyclooxygenase (cox) enzymes, reducing the production of prostaglandins

EXAMPLE

- Ibuprofen
- Naproxen
- ketoprofen
- Flurbiprofen

Therapeutic Uses

- Pain Relief
- Anti Inflammatory
- Antipyretic

2 FENAMATE

- Fenamate are subclass of Non- Selective Cox Inhibitors derived from Anthranilic Acid.
- They are characterized by their ability to reduce inflammation, pain and fever, primarily through inhibition of Cox enzyme. which decreases the production of prostaglandins.

Examples

- Mefenamic Acid
- Flufenamic Acid
- Tolfenamic Acid

ⓓ Enolic Acid Derivative

- They are another subclass of Non Selective Cox Inhibitors primarily work by inhibiting Cox enzymes, reducing prostaglandin synthesis & thereby alleviating inflammation, pain & fever.
- They are characterized by their enolic acid structure & are commonly used for managing chronic inflammatory conditions.

Examples

- Piroxicam
- Meloxicam
- Tenoxicam
- Lornoxicam

© Acetic Acid Derivatives

- Acetic Acid Derivatives are a group of Non-steroidal Anti-Inflammatory Drugs that are structurally derived from acetic acid.
- These drugs inhibit cyclooxygenase (Cox) enzymes, reducing prostaglandin synthesis to relieve inflammation, pain & fever.
- They are known for their strong anti-inflammatory effects & commonly used for acute & chronic inflammatory conditions.

Examples

- Ketorolac
- Indomethacin
- Nabumetone
- Etodolac

(F) PYRAZOLONE DERIVATIVE

- Pyrazolone derivatives are a class of Non-selective cox inhibitors that are chemically related to pyrazolone, a heterocyclic compound.
- These derivatives have anti-inflammatory, analgesic & antipyretic properties, similar to other NSAIDs. and are used to treat conditions like pain, inflammation & fever.

Examples

- Phenylbutazone
- Oxyphenbutazone

② PREFERENTIAL COX-II INHIBITORS

Preferential Cox-2 Inhibitors are a class of Nonsteroidal anti-inflammatory drugs that specifically target & inhibit the Cox-2 enzyme more than Cox-1 enzyme.

MOA

- Preferential Cox-2 inhibitors are designed to mainly inhibit Cox-2 enzyme, which is primarily responsible for production of pro-inflammatory prostaglandins.
- While they primarily target Cox-2, they may also inhibit Cox-1 to a lesser degree.

PHARMACOKINETICS

- Absorption : They are well absorbed orally.
- Distribution : These drugs are widely distributed throughout the body
- Metabolism : They are metabolized in liver primarily by Cytochrome P450 enzymes
- Excretion : They are excreted via kidneys

Examples

- Nimesulide
- Diclofenac
- Aceclofenac
- Meloxicam
- Etodolac

③ SELECTIVE COX-2 INHIBITORS

Selective cox-2 inhibitors are a class of drugs designed to specifically target & inhibit the cox-2 enzyme, which plays a key role in production of pro-inflammatory prostaglandins.

MOA

- cox-2 inhibitors work by binding to the active site of cox-2 enzyme & preventing its action.
- This inhibition reduces the synthesis of prostaglandins, particularly prostaglandin E2, which is involved in mediating pain, fever and inflammation.

PHARMACOKINETICS

- Absorption : They are well absorbed from GIT.
- Distribution : They are highly protein-bound, which affects their distribution in the body.
- Metabolism : Most cox-2 inhibitors are metabolized in the liver by cytochrome P450 enzymes.
- Excretion : Drugs are primarily excreted through urine.

EXAMPLES

- Celecoxib
- Etoricoxib
- Parecoxib

④ Analgesic- Antipyretics With Poor Antiinflammatory Action

Analgesic Antipyretics with poor anti- inflammatory action primarily provide relief from pain & fever reduction but have minimal or no impact on inflammation.

Mechanism Of Action

- These drugs typically inhibit COX enzymes, particularly in CNS, reducing production of prostaglandins that mediate pain & fever.
- Unlike NSAIDs, they have weak peripheral COX inhibition, which limits their anti- inflammatory properties.

Examples

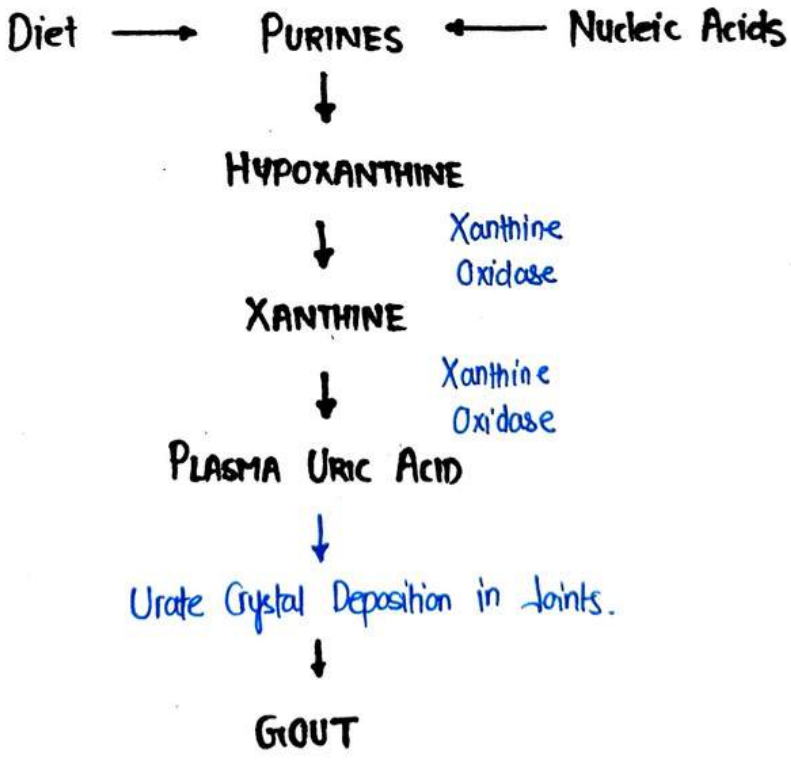
- Paracetamol
- Metamizol
- Nefopam

GOUT

- Gout is a type of Arthritis caused by buildup of Uric Acid crystals in joints.
- It typically leads to sudden & severe episodes of pain, swelling, redness, often in big toe. but can affect other joints as well

CAUSES

Gout occurs when uric acid, a waste product from breakdown of purines (found in foods & body) accumulates in blood (hyperuricemia) This leads to crystal deposits in joints.



Risk Factors

- Diet : High in Purines (Red Meat, Alcohol, Shellfish, Sugary Drinks etc)
- Genetics : Family history of Gout
- Medical Conditions : Obesity, Hypertension, Diabetes, kidney disease
- Medications : Diuretics, aspirin & others.

Symptoms

- Intense joint pain
- Swelling
- Redness
- Stiffness

Anti Gout Drugs

Anti Gout drugs are medications / agents that are used in the treatment of Gout.

Classification

① For Acute Gout

- NSAIDs
- Colchicine
- Glucocorticoids

② For Chronic Gout

ⓐ Uricosurics

- ~~Rr~~ Probenecid
- Sulfinpyrazone

ⓑ Synthesis Inhibitors

- Allopurinol
- Febuxostat

FOR ACUTE GOUT

① NSAIDs

- NSAIDs (Non Steroidal Anti Inflammatory Drugs) are commonly used to treat pain & inflammation associated with Gout, especially during acute attacks.
- They work by reducing inflammation in afflicted joint & providing rapid relief from symptoms.

MOA

- NSAIDs inhibits COX 1 & COX2 enzymes which are involved in producing prostaglandins.
- Prostaglandins are substances that contribute to inflammation & pain in joints.

Common NSAIDs Used For Gout

- Indomethacin
- Naproxen
- Ibuprofen
- Diclofenac
- Celecoxib

ⓑ COLCHICINE

- Colchicine is a medication widely used for treatment & prevention of Gout.
- It is particularly effective for Acute Gout when administered early.

MOA

- Colchicine disrupts microtubules polymerization by binding to tubulin.
- This inhibits the migration & activity of neutrophills at site of inflammation.
- It reduces the release of inflammatory mediators like IL-1, which is heavily involved in inflammatory response in Gout.
- Importantly, Colchicine does not affect uric acid levels, its action is purely anti-inflammatory.

PHARMACOKINETICS

- Absorption : Rapidly absorbed in gastrointeshinal tract.
- Distribution : It is widely distributed in tissues.
- Metabolism : Metabolized primarily in liver through CYP3A4 enzymes.
- Excretion : Eliminated through Urine & Feces.

© GLUCOCORTICOIDS

- Glucocorticoids are an effective option for treating Gout, especially in patients who cannot tolerate NSAIDs or Colchicine.
- They act as potent anti-inflammatory agents and are commonly used to manage acute gout flares.

MOA

- It inhibits the production of pro-inflammatory cytokines like IL-1, IL-6 etc.
- It decrease the recruitment & activation of neutrophils and monocytes at the site of inflammation. and also inhibits Phospholipase A2.

FOR CHRONIC GOUT

@ Uricosurics

- Uricosurics are a class of medications used in the treatment of gout to reduce serum uric acid levels by increasing its excretion through the kidneys.
- These drugs are effective for patients who overproduce or underexcrete uric acid and are an important option for long-term gout management.

MOA

- Uric acid is filtered at glomerulus, with most being reabsorbed in proximal tubules.
- Uricosurics blocks URAT1 transporter in proximal renal tubules.
- This inhibition decreases uric acid reabsorption, leading to increased excretion in urine.

EXAMPLES

- Probenecid
- Sulfinpyrazone

ⓑ SYNTHESIS INHIBITOR

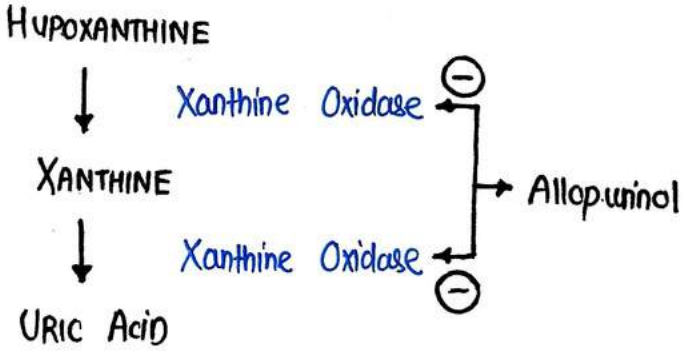
Synthesis Inhibitors for gout target the production of Uric Acid by inhibiting the enzyme Xanthine Oxidase, which is a key enzyme in Purine Metabolism.

Allopurinol

- Allopurinol is a xanthine oxidase inhibitor used as a first-line treatment for the long-term management of Gout & hyperuricemia.
- It lowers serum uric acid levels by inhibiting Uric Acid synthesis thereby prevents Gout flares.

MOA

Allopurinol is a purine analogue that inhibits xanthine oxidase.



PHARMACOKINETICS

- Absorption : Rapidly absorbed after oral administration.
- Metabolism : Metabolized in liver to Oxypurinol, an active metabolite that also inhibits xanthine oxidase.
- Excretion : Primarily excreted by kidneys with half-life 1-2 hours.

RHEUMATOID ARTHRITIS

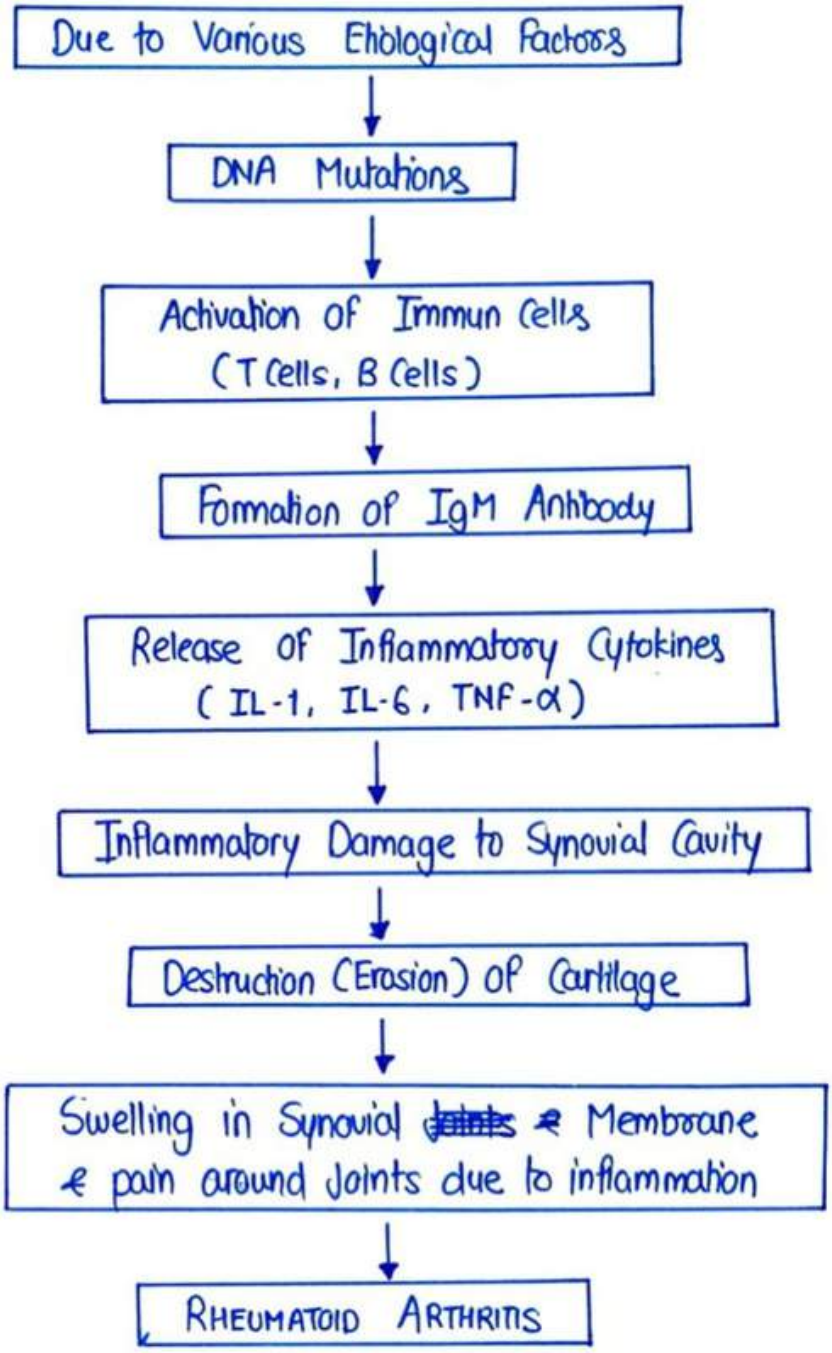
- Rheumatoid Arthritis is a chronic autoimmune disorder characterized by inflammation of joints.
- In Rheumatoid Arthritis, the body's immune system mistakenely attacks the synovium, the lining of joints, leading to pain, swelling, stiffness & inflammation.
- If Rheumatoid Arthritis not treated early, it will lead to progressive joint deformity.

Causes

The exact cause of reheumatoid arthritis is not fully understood, but it is belived to result from a combination of genetic, environmental & hormonal factors

- Genetic Predisposition :
- Certain genes related to immune system (e.g. HLA - DRB1) can increase risk of developing RA.
- Environmental factors
- Smoking
- Hormal Imbalances
- Age

Pathogenesis



Sign & Symptoms

- Fatigue
- Weakness
- Joint Pain
- Swelling
- Shiffness
- Loss of Joint Functions.

Complications

- Osteoporosis
- Infections
- Cardiovascular Issues
- Premature Death

Treatment

- Medications :
  - NSAIDs
  - Corticosteroids
- Surgical Approach
- Physical Exercise
- Balanced Diet.

CLASSIFICATION OF ANTIRHEUMATIC DRUGS

Antirheumatic drugs can be classified as follows:

① Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

- **Synthetic DMARDs**

ⓐ Conventional Synthetic DMARDs

- Methotrexate
- Sulfasalazine
- Hydroxychloroquine
- Leflunomide

ⓑ Targeted Synthetic DMARDs

- Tofacitinib
- Baricitinib
- Upadacitinib

- **Biological DMARDs**

ⓐ Tumor Necrosis Factor Inhibitors (TNF): Etanercept, Infliximab, Adalimumab

ⓑ Interleukin (IL) Inhibitors: Anakinra, Tocilizumab

ⓒ Costimulation Modulators: Abatacept

ⓓ B Cell Inhibitors: Rituximab

② NSAIDs

- Ibuprofen
- Naproxen
- Celecoxib

③ Corticosteroids

- Prednisone
- Methylprednisolone

④ Analgesics

- Acetaminophen
- Tramadolal
- Oxycodone

⑤ Adjunctive Therapies

- Vitamin D & Calcium
- Biphosphonates

① Disease Modifying Anti Rheumatic Drugs

- DMARDs are class of medications used to treat Rheumatoid Arthritis.
- Unlike pain relievers or anti-inflammatory drugs, DMARDs don't just manage symptoms - they work to slow or stop the progression of disease by targeting the underlying immune system responses that causes inflammation & tissue damage.
- They are of mainly two types:

ⓐ Synthetic DMARDs
ⓑ Biological DMARDs

ⓐ Synthetic DMARDs

- They are chemically manufactured drugs that work to modify the underlying autoimmune disease.
- They are further divided into two subtypes:

(1) Conventional Synthetic DMARDS
(2) Targeted Synthetic DMARDs

(1) Conventional Synthetic DMARDs

Conventional synthetic DMARDs are class of medications used to treat autoimmune diseases like rheumatoid arthritis.

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They show broad immunosuppressive and anti-inflammatory effects but do not act on specific molecular targets.

Drugs

Methotrexate, Sulfasalazine, Hydroxychloroquine, Leflunomide, Cyclophosphamide.

(2) Targeted Synthetic DMARDs

Targeted synthetic DMARDs are newer class of drugs designed to more precisely target specific molecules or pathways involved in immune response & inflammation, particularly in rheumatoid arthritis

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- They targeted synthetic DMARDs work by blocking specific enzymes or proteins that play a central role in inflammatory process.
- Example : Janus kinase (JAK) inhibitors.

JAK Inhibitors

- Janus kinase are enzymes are involved in signalling pathways for various immune cells, which are central to the inflammatory processes in autoimmune diseases.
- JAK inhibitors block these enzymes, disrupting inflammatory signals that contribute to disease activity.

Examples

- Tofacitinib
- Baricitinib
- Upadacitinib

(b) BIOLOGICAL DMARDs

They are biologically derived protein-based drugs that target specific components of immune system.

(1) TNF-α Inhibitors

- They block TNF (~~Tissue~~ Tumor Necrosis Factor- alpha) a pro-inflammatory cytokine that plays a central role in inflammatory process of autoimmune disease.
- Example : ~~Adalam~~ Adalimumab, Infliximab, Golimumab.

(2) Interleukin Inhibitors

- Targets IL-1 or IL-6, which plays a key role in inflammation.
- IL-1 Inhibitor : Anakinra
- IL-6 Inhibitor : Tocilizumab

(3) Costimulation Modulators

- These are the drugs that inhibit T-cell activation
- Example : Abatacept

(4) B-Cell Depleting Agent

- They reduce B-cell activity to suppress autoimmune responses.
- Example : Rituximab.

② NSAIDs

NSAIDs are class of drugs that reduce inflammation, pain & fever associated with rheumatoid arthritis.

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They work by reducing the production of Prostaglandins a pro inflammatory mediator by inhibiting Cox enzymes.

Drugs

- Ibuprofen
- Naproxen
- Diclofenac
- Celecoxib.
- Indomethacin etc.

③ CORTICOSTEROIDS

- Corticosteroids are type of anti-inflammatory medications used in treatment of RA.
- However they are typically not used as long-term therapy due to potential side effects.

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- Corticosteroids, such as prednisone are synthetic version of hormonal cortisol, naturally produced by adrenal gland.
- They suppress the function of various immune cells (like T-cells, B cells & Macrophages) & various cytokines, reducing inflammation attack on joints.

Example

- Prednisone
- Methylprednisolone
- Hydrocortisone

④ ANALGESICS

- In treatment of RA, Analgesics play an important role in managing pain & improving quality of life but lack anti-inflammatory or disease modifying properties.

Examples

- Acetaminophen
- Opoids
  - Morphine
  - Oxycodone
  - Hydrocodone

⑤ ADJUNCTIVE THERAPIES

Used to manage side effects of treatment or complication.

- Vitamin D & Calcium : To prevent corticosteroid-induced Osteoporosis
- Bisphosphonates: For osteoporosis prevention.

THANK YOU

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