Unit-3
Pharmacology- II

B.Pharma 5th Sem Notes

Unit: 3

- **Autocoids and related drugs**
  - Introduction to autacoids and classification
  - Histamine, 5-HT and their antagonists.
  - Prostaglandins, Thromboxanes and Leukotrienes.
  - Angiotensin, Bradykinin and Substance P.
  - Non-steroidal anti-inflammatory agents
  - Anti-gout drugs
  - Antirheumatic drugs

Introduction to Autacoids and Classification

Autacoids:

- **Autacoids** are locally acting bioactive molecules synthesized in various tissues, functioning as "local hormones" to regulate physiological and pathological processes.
- Derived from the Greek *autos* (self) and *akos* (remedy), they act near their site of production, exerting paracrine or autocrine effects. Unlike classical hormones, autacoids are not secreted by glands but are involved in inflammation, immunity, pain, and homeostasis.

Classification:

Autacoids are categorized based on chemical structure:

1. **Amine Autacoids**:
    - Derived from amino acids.
    - Examples: *Histamine* (from histidine; mediates allergies, gastric secretion) and *Serotonin (5-HT)* (from tryptophan; regulates mood, digestion).
2. **Eicosanoids**:
    - Lipid-derived from arachidonic acid via cyclooxygenase (COX) or lipoxygenase (LOX) pathways.
    - Examples: *Prostaglandins* (inflammation, pain), *Leukotrienes* (asthma, allergies), and *Thromboxanes* (blood clotting).
3. **Peptide Autacoids**:
    - Protein-based molecules.
    - Examples: *Bradykinin* (vasodilation, pain), *Cytokines* (immune signaling), and *Angiotensin* (blood pressure regulation).

Histamine

1. Definition

- Histamine is a **biogenic amine** derived from the amino acid **L-histidine**. It acts as a **local hormone (autacoid)** and **neurotransmitter**, playing important roles in immune responses, inflammation, gastric acid secretion, and neurotransmission.

Storage of Histamine

Histamine is stored in the following places in the body:

1. **Mast Cells**: These are large cells located in connective tissue, especially near blood vessels, skin, lungs, and mucous membranes. Histamine is stored in granules within mast cells and is released in response to various stimuli, including allergens, injury, or infection.
2. **Basophils**: These are a type of white blood cell that also store histamine in granules and release it during immune responses.
3. **Enterochromaffin Cells**: Located in the gastrointestinal tract, these cells store and release histamine, where it plays a role in regulating gastric acid secretion.
4. **Brain**: In the CNS, histamine is synthesized and stored by specific neurons that release it as a neurotransmitter to influence wakefulness, cognitive function, and appetite regulation.

Histamine is stored in these cells bound to acidic proteins, and its release is tightly controlled. The storage and release mechanisms are regulated by various enzymes and receptors, ensuring histamine is available when needed but not constantly active.

Pharmacological Role of Histamine

Histamine exerts its effects through the activation of histamine receptors, which are classified into four main subtypes: H1, H2, H3, and H4. Each of these receptors is associated with different physiological functions.

1. **H1 Receptors (Allergic Responses)**:
    - **Location**: Primarily found in smooth muscles, endothelial cells, and the central nervous system (CNS).
    - **Pharmacological Role**:

- Mediates allergic reactions (e.g., hay fever, urticaria).
- Causes vasodilation, increased vascular permeability, and smooth muscle contraction, contributing to the classic symptoms of an allergic response (redness, swelling, itching).
- Involved in the contraction of bronchial smooth muscle (leading to bronchoconstriction) in asthma.
- In the CNS, histamine acts as a neurotransmitter to influence the sleep-wake cycle and cognitive functions.

2. **H2 Receptors (Gastric Acid Secretion)**:
   - **Location**: Primarily found on parietal cells in the stomach lining.
   - **Pharmacological Role**:
     - Histamine binds to H2 receptors in the stomach, stimulating the parietal cells to secrete gastric acid.
     - This process is important for the digestion of food and the absorption of nutrients.
     - H2 receptor activation also plays a role in maintaining gastric pH and protecting the stomach lining from pathogens.
3. **H3 Receptors (Neurotransmission Regulation)**:
   - **Location**: Found mainly in the brain and the central nervous system.
   - **Pharmacological Role**:
     - H3 receptors are involved in the regulation of histamine release within the brain and the release of other neurotransmitters, such as dopamine, serotonin, and acetylcholine.
     - They play a role in regulating sleep-wake cycles, cognitive processes, and appetite.
     - Activation of H3 receptors generally inhibits the release of histamine and other neurotransmitters, thereby modulating neurotransmission and maintaining balance in the CNS.

4. **H4 Receptors (Immune Response)**:
    - **Location**: Predominantly found in immune cells, such as mast cells, eosinophils, and neutrophils.
    - **Pharmacological Role**:
        - Histamine binding to H4 receptors influences the immune system by promoting chemotaxis (the movement of immune cells toward sites of infection or injury).
        - H4 receptors play a role in inflammatory responses, allergy development, and autoimmune reactions.

Pharmacological Effects of Histamine

Histamine's pharmacological roles are highly context-dependent and include both beneficial and harmful effects:

- **Vasodilation and Increased Vascular Permeability**: In allergic reactions, histamine causes vasodilation and increases the permeability of blood vessels, leading to fluid leakage and the characteristic swelling and redness of inflammation.
- **Bronchoconstriction**: Histamine induces smooth muscle contraction in the bronchi, leading to narrowing of the airways, which is a key factor in allergic asthma.
- **Gastric Acid Secretion**: Histamine promotes the secretion of gastric acid, which aids in digestion but can contribute to conditions such as peptic ulcers and gastroesophageal reflux disease (GERD) when overproduced.
- **Neurotransmitter Functions**: In the brain, histamine plays a role in wakefulness, attention, and appetite regulation. Its dysregulation can contribute to sleep disorders and cognitive dysfunctions.

5-HT (Serotonin) and Its Antagonists

1. Introduction to 5-HT (Serotonin)

- **Chemical Structure**: 5-Hydroxytryptamine (5-HT), a monoamine neurotransmitter derived from the amino acid tryptophan.
- **Synthesis**:
  - **Pathway**: Tryptophan → 5-HTP (via tryptophan hydroxylase) → Serotonin (via aromatic L-amino acid decarboxylase).
  - **Storage**: Packaged into vesicles in presynaptic neurons; released into synaptic clefts upon stimulation.
- **Physiological Roles**:
  - **CNS**: Mood regulation (e.g., depression, anxiety), sleep-wake cycles, appetite, cognition, and pain perception.
  - **Peripheral Systems**: Gastrointestinal motility, vasoconstriction/dilation, platelet aggregation, and nausea/vomiting reflexes.

2. 5-HT Receptor Subtypes

Serotonin receptors are classified into seven families (5-HT_1 to 5-HT_7), most being G-protein coupled receptors (GPCRs), except 5-HT_3 (ligand-gated ion channel).

Receptor	Signaling Pathway	Location	Key Functions
5-HT_1 (A, B, D)	Gi/Go (↓ cAMP)	CNS, blood vessels	Mood, anxiety, vasoconstriction (e.g., 5-HT_1B/$_1$D in migraines)
5-HT_2 (A, B, C)	Gq (↑ IP_3/DAG)	CNS, smooth muscle, platelets	Hallucinations, vascular contraction, platelet aggregation
5-HT_3	Ligand-gated Na^+/K^+ channel	GI tract, CNS	Nausea, vomiting, visceral pain
5-HT_4	Gs (↑ cAMP)	GI tract, CNS	GI motility, cognitive enhancement

5-HT$_{5}$/6/7	Gs/Gi	CNS	Mood, circadian rhythms, memory

3. 5-HT Antagonists

Definition: Drugs that block serotonin receptors, preventing 5-HT binding and downstream effects.

Classification by Receptor Subtype

1. **5-HT$_3$ Antagonists**:
   - **Examples**: Ondansetron, Granisetron, Palonosetron.
   - **Uses**: Chemotherapy/radiation-induced nausea, post-operative nausea.
   - **Side Effects**: Headache, constipation, dizziness.
2. **5-HT$_2$ Antagonists**:
   - **5-HT$_2$A**:
     - **Examples**: Risperidone (antipsychotic), Trazodone (antidepressant), Cyproheptadine (serotonin syndrome).
     - **Uses**: Schizophrenia, depression, insomnia, allergic reactions.
     - **Side Effects**: Weight gain, sedation, metabolic changes.
   - **5-HT$_2$C**:
     - **Example**: Mirtazapine (also blocks 5-HT$_3$).
     - **Uses**: Depression, appetite stimulation.
3. **5-HT$_1$ Antagonists**:
   - **Examples**: Pindolol (partial 5-HT$_1$A antagonist, used in research), Methysergide (5-HT$_1$B/$_1$D antagonist, withdrawn due to toxicity).
   - **Uses**: Investigational for anxiety/depression; historical use in migraines.
4. **5-HT$_4$ Antagonists**:
   - **Example**: Piboserod (investigational).

- **Uses**: Potential in IBS and heart failure (limited clinical use).

5. **Non-Selective Antagonists**:
   - **Example**: Cyproheptadine (blocks 5-HT_2, H_1, and muscarinic receptors).
   - **Uses**: Serotonin syndrome, allergies.

Pharmacological action:

Pharmacological action on CNS:

- 5 HT act as a neurotransmitter.
- Regulate mood behavior , sleep, depression pain, thermoregulation.
- Regulate sleep cycle by synthesis of melatonin.
- Do not cross blood brain barrier if injective I.V.

Pharmacological action on CVS:

- Contraction of vascular smooth muscle (Except skeletal and heart muscle).
- In skeletal and heart muscle is causes vasodilation and bradycardia.
- 5 HT causes platelet aggregation (weak) by $5HT_{2A}$ receptor.

Pharmacological action on GIT:

- Stimulate peristalsis and gastric secretion.
- Stimulate mucous secretion hence designated as ulcer protective.
- Over production of 5HT leads to tumor of enterochromaffin cells (associated with severe diarrhea).

Pharmacological action on other organ:

- Stimulate pain perception and itching by $5HT_3$ on afferent nerve.
- Constrict bronchial smooth muscle by less potent then histamine.
- Reduces food intake.

Prostaglandins, Thromboxanes and Leukotrienes

Eicosanoids:

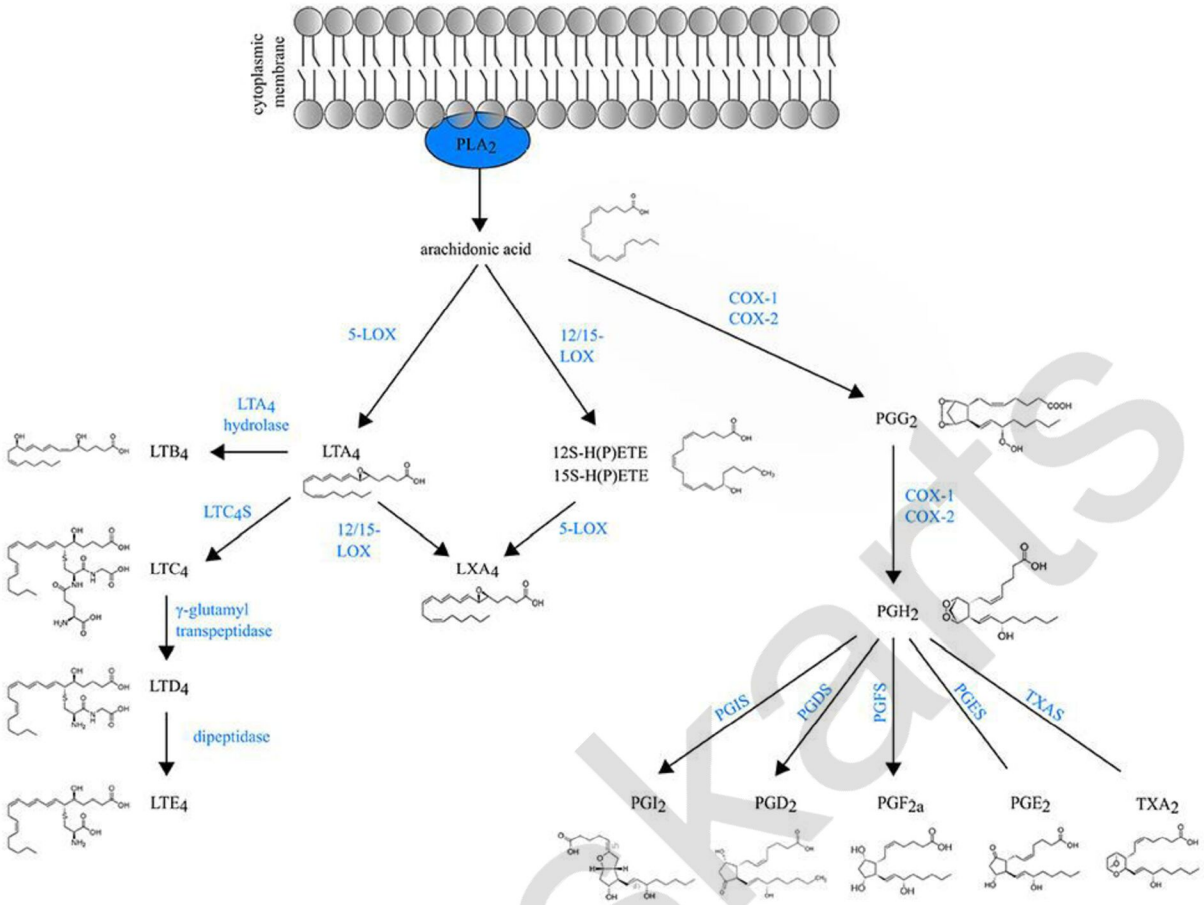
Eicosanoids are 20 carbon (eicosa referring to 20 in greek) unsaturated fatty acids derived mainly from arachidonic acid in the cell membrane.

The principal eicosanoids are prostaglandins (PG), Prostocyclin (PGI_2), Thromboanes (TX) and Leukotrienes (LT).

- Major families of eicosanoids:
    - Prostanoids:
        - **Thromboxanes (TXA_2s)**
        - **Prostaglandins (PGs)**
        - **Prostacyclin (PGI_2)**
    - **Leukotrienes (LTs)** and **lipoxins (LXs)**
- Receptor names: Receptor classification system uses the distinguishing letter of the prostanoid (e.g., "E" in prostaglandin E) and combines it with the letter "P" for prostanoid. (e.g., PGE has EP receptors). Subscript numerals represent the subtypes (e.g., $PGE_2 = EP_2$).

Biosynthesis:

- Eicosanoids are typically not stored within cells.
- Synthesis is on-demand and is affected by physical, chemical, and hormonal stimuli.
- With proper stimuli, specific pathways are triggered to produce different eicosanoid families.
- Stimuli → phospholipases activated → arachidonic acid is released
- Arachidonic acid is metabolized by different enzyme pathways:
    - **LOX** → LT and LX
    - **COX** → cyclization to PGI_2, PG, or TXA_2
        - COX-1: enzyme constitutively expressed in many tissues
        - COX-2: enzyme induced by pro-inflammatory cytokines and found in the brain, kidney, bone, and female reproductive system



Thromboxanes

- Metabolite of arachidonic acid synthesized in platelets
- Generated through the following process:
  - Arachidonic acid → prostaglandin H_2 (PGH_2) via enzymes COX-1/COX-2
  - TXA_2 is predominantly COX-1 derived.
  - PGH_2→ TXA_2 via the action of TXA_2 synthase (TXAS)
- Receptors: TPα and β (expressed in different tissues and cells including platelets, vascular endothelial cells, lungs, kidneys, heart, thymus, and spleen)

Effects:

- Activates phospholipase A_2
- Platelet activation:
  - Platelet aggregation
  - Platelet shape change

- Platelet degranulation of dense granules and alpha granules
- Vasoconstriction

Clinical correlation:

Inflammatory effects of TXA_2 in some conditions:

- Thrombosis:
- Increased levels of TXA_2 are noted in injury and inflammation.
- ↑ Platelets activation, aggregation, and vasoconstriction → thrombosis
- Conditions related to thrombosis:
  - Myocardial infarction and angina
  - Atherosclerosis
- Asthma: TXA_2 is related to bronchoconstriction and airway remodeling.

Prostaglandins

- Produced from arachidonic acid via COX:
  - Basal amounts of PGs are produced through the action of COX-1.
  - Mediators (e.g., cytokines) induce the COX-2 isoform → ↑ PG production

Arachidonic acid → PGH2 (common substrate for TXA2 and PGs)

From PGH2, different enzymes produce varying PGs:

- Names of PGs are based on structural features, coded by a letter (e.g., PGD, PGE, PGI).
- Subscript numeral indicates the number of double bonds (e.g., PGE1, PGE2).

Receptors:

- Prostaglandin E (PGE): E-type prostanoid (EP) 1–4 receptors
- Prostaglandin D2 (PGD2): D-type prostanoid (DP) 1 and 2 receptors
- Prostaglandin F2α (PGF2α): F-type prostanoid (FP) receptors
- PGI_2: I-type prostanoid (IP) receptors

Effects:

Table: Effects of prostaglandins	
Prostaglandins	**Effects**
PGD_2 (made predominantly by mast cells)	• Vasodilation • Chemotaxis
PGE_1	• Vasodilation • ↓ Production of gastric acid • Uterine contraction (↑ tone)

PGE_2	• Vasodilation
	• Inflammation:
	  ○ Pain (hyperalgesic)
	  ○ Arterial dilatation (redness)
	  ○ Swelling (↑ microvascular permeability)
	• Uterine contraction (↑ tone in low concentrations)

$PGF_2\alpha$	• Uterine contraction (↑ tone) • Relaxation of ciliary muscle
PGI_2 (produced by vascular wall endothelial cells)	• Vasodilation • Inhibitor of platelet aggregation • Potentiates effects (↑ permeability and Chemotaxis) of other mediators

Leukotrienes and Lipoxins

- End-products of the LOX pathway
- Arachidonic acid is converted to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) by 5-LOX:
  - 5-HPETE → 5-hydroxyeicosatetraenoic acid (5-HETE) → leukotriene A_4 (LTA_4)
  - By the action of LOX, LTA_4 is converted to LTB_4, cysteinyl LTs (LTC_4, LTD_4, LTE_4) or LX.
  - In some cells utilizing different LOX pathways, arachidonic acid can be converted to LXs without conversion to LTA_4.

Receptors:

- Cysteinyl leukotrienes: CysLT receptors
- LTB4: leukotriene B (BLT) receptors.

Effects

Leukotrienes mediate allergic and inflammatory responses with release stimulated by allergens.

Table: Effects of eicosanoids	
Eicosanoids	**Effects**
LTC_4, LTD_4, LTE_4	• ↑ Vascular permeability • Bronchoconstriction • Vasoconstriction
LTB_4 (and HETE)	• Leukocyte adhesion • Chemotaxis (neutrophils and eosinophils)
LXs A_4 and B_4	• Anti-inflammatory • Inhibit leukocyte adhesion and chemotaxis

Clinical correlation

Leukotrienes are released from cells and their Inflammatory effects are seen in asthma and allergies.

- Cysteinyl LTs:
  - Formed from eosinophils and mast cells, which are commonly associated with asthma
  - ↑ Mucus production
  - Bronchoconstriction (smooth muscle contraction)
- While less well-defined in asthma, LTB4 is a chemoattractant for both neutrophils and eosinophils.

Angiotensin, Bradykinin and Substance P.

Introduction to Angiotensin:

Angiotensin is a peptide hormone that plays a critical role in regulating blood pressure, fluid balance, and electrolyte homeostasis. It is a key component of the **renin-angiotensin-aldosterone system (RAAS)**, which is a hormone system that regulates blood pressure and fluid balance. Angiotensin exists in several forms, with **angiotensin II (Ang II)** being the most biologically active.

Types of Angiotensin Receptors

Angiotensin exerts its effects by binding to specific receptors on the surface of target cells. The two primary types of angiotensin receptors are:

1. **AT1 Receptor (Angiotensin II Type 1 Receptor)**:
    - Found in the heart, blood vessels, kidneys, adrenal glands, and brain.
    - Mediates most of the physiological effects of angiotensin II, including vasoconstriction, aldosterone release, and sodium retention.
2. **AT2 Receptor (Angiotensin II Type 2 Receptor)**:
    - Less well understood compared to AT1.
    - Generally opposes the actions of AT1 receptors, promoting vasodilation, natriuresis (sodium excretion), and anti-proliferative effects.

Synthesis of Angiotensin

The synthesis of angiotensin involves a series of enzymatic reactions:

1. **Production of Angiotensinogen**:
    - Angiotensinogen, a glycoprotein, is synthesized and secreted primarily by the liver.
    - It serves as the precursor for angiotensin peptides.
2. **Conversion to Angiotensin I**:

- **Renin**, an enzyme released by the kidneys in response to low blood pressure, low sodium levels, or sympathetic nervous system activation, cleaves angiotensinogen to produce **angiotensin I (Ang I)**.
- Angiotensin I is a decapeptide (10 amino acids) with minimal biological activity.

3. **Conversion to Angiotensin II**:
   - **Angiotensin-converting enzyme (ACE)**, primarily found in the lungs, converts angiotensin I to **angiotensin II (Ang II)**, an octapeptide (8 amino acids).
   - Angiotensin II is the most potent vasoconstrictor in the RAAS and has multiple physiological effects.
4. **Alternative Pathways**:
   - Angiotensin II can also be formed via non-ACE pathways, such as through the action of **chymase** or other proteases.

Metabolism of Angiotensin

Angiotensin II is metabolized into smaller peptides, which may have their own biological activities:

1. **Degradation to Angiotensin III**:
   - Angiotensin II is converted to **angiotensin III (Ang III)** by the removal of one amino acid (aspartate) by aminopeptidases.
   - Angiotensin III retains some biological activity, particularly in stimulating aldosterone release.
2. **Degradation to Angiotensin IV**:
   - Further degradation of angiotensin III produces **angiotensin IV (Ang IV)**, a hexapeptide.
   - Angiotensin IV has been implicated in cognitive functions and renal blood flow regulation.
3. **Inactivation**:
   - Angiotensin peptides are eventually broken down into inactive fragments by various peptidases in the blood and tissues.

Physiological Roles of Angiotensin II

- **Vasoconstriction**: Angiotensin II binds to AT1 receptors on vascular smooth muscle, causing vasoconstriction and increasing blood pressure.
- **Aldosterone Release**: It stimulates the adrenal cortex to release aldosterone, which promotes sodium and water retention in the kidneys.
- **Thirst and ADH Release**: Angiotensin II acts on the brain to increase thirst and stimulate the release of antidiuretic hormone (ADH), promoting water retention.
- **Cardiac and Vascular Remodeling**: Chronic activation of the RAAS can lead to hypertrophy of cardiac and vascular tissues, contributing to hypertension and heart failure.

Clinical Significance

- **Hypertension**: Overactivity of the RAAS is a major contributor to hypertension. Drugs targeting this system, such as **ACE inhibitors** and **angiotensin receptor blockers (ARBs)**, are commonly used to treat high blood pressure.
- **Heart Failure and Kidney Disease**: RAAS inhibitors are also used in the management of heart failure and chronic kidney disease to reduce the progression of these conditions.

Bradykinin:

Introduction to Bradykinin

- **Bradykinin** is a potent vasoactive peptide that plays a central role in inflammation, pain perception, and vascular homeostasis.
- It is a key component of the **kinin-kallikrein system**, which interacts with other systems, such as the renin-angiotensin-aldosterone system (RAAS), to regulate blood pressure, vascular permeability, and immune responses.
- Bradykinin is particularly known for its vasodilatory effects, counteracting the vasoconstrictive actions of angiotensin II.

Types of Bradykinin Receptors

Bradykinin exerts its effects by binding to two main G protein-coupled receptors:

1. **Bradykinin B2 Receptor (B2R)**:
    - **Constitutively expressed** in most tissues, including blood vessels, kidneys, and nervous system.
    - Mediates acute responses such as vasodilation, pain, and increased vascular permeability.
    - Activated by intact bradykinin and its immediate metabolites.
2. **Bradykinin B1 Receptor (B1R)**:
    - **Inducible** under inflammatory conditions (e.g., tissue injury, cytokines).
    - Preferentially binds to **des-Arg⁹-bradykinin**, a metabolite of bradykinin.
    - Involved in chronic inflammation, hyperalgesia, and immune cell recruitment.

Synthesis of Bradykinin

Bradykinin is generated through enzymatic cleavage of its precursor protein:

1. **Kininogen Precursors**:

- **High-molecular-weight kininogen (HMWK)** and **low-molecular-weight kininogen (LMWK)** are synthesized in the liver.
- HMWK is the primary substrate for bradykinin production.

2. **Release of Bradykinin**:
   - **Tissue kallikrein** or **plasma kallikrein** cleaves HMWK to release **bradykinin** (a nonapeptide: 9 amino acids).
   - Kallikrein activation is triggered by tissue damage, inflammation, or contact with foreign surfaces (e.g., in the coagulation cascade).

Metabolism of Bradykinin

Bradykinin has a **short half-life** (seconds to minutes) and is rapidly degraded by peptidases:

1. **Angiotensin-Converting Enzyme (ACE)**:
   - ACE inactivates bradykinin by cleaving two amino acids from its C-terminus.
   - **ACE inhibitors** (e.g., lisinopril) block this degradation, leading to bradykinin accumulation (explaining side effects like cough and angioedema).
2. **Other Enzymes**:
   - **Aminopeptidase P (APP)**, **carboxypeptidase N (CPN)**, and **neutral endopeptidase (NEP)** further degrade bradykinin into inactive fragments.
3. **Metabolites**:
   - **Des-Arg⁹-bradykinin** (active at B1 receptors) and smaller inactive peptides.

Physiological Roles of Bradykinin

1. **Vasodilation**:
   - Stimulates nitric oxide (NO) and prostacyclin release, lowering blood pressure.

2. **Increased Vascular Permeability**:
    - Promotes edema and leukocyte migration to sites of injury.
3. **Pain and Inflammation**:
    - Activates sensory neurons (via B2 receptors), inducing pain and hyperalgesia.
4. **Bronchoconstriction**:
    - Can cause airway narrowing in asthma or anaphylaxis.
5. **Renal Function**:
    - Enhances sodium excretion and modulates renal blood flow.

Clinical Significance

1. **Hereditary Angioedema (HAE)**:
    - Caused by **C1 esterase inhibitor deficiency**, leading to uncontrolled bradykinin production and recurrent swelling.
    - Treated with **B2 receptor antagonists** (e.g., icatibant) or C1 inhibitor replacements.
2. **ACE Inhibitor Side Effects**:
    - Accumulation of bradykinin due to ACE inhibition can cause **cough** and **angioedema**.
3. **Inflammatory Diseases**:
    - Overactive bradykinin signaling contributes to chronic inflammation, sepsis, and arthritis.
4. **Therapeutic Targets**:
    - **B2 receptor antagonists** and **kallikrein inhibitors** are under investigation for treating HAE, hypertension, and inflammatory conditions.

Substance P:

- Substance P is a peptide which belongs to the tachykinin family of peptides.
- It acts as a neurotransmitter in the CNS and the enteric nerve plexus.
- Neurokinin A & neurokinin B are other members of tachykinin family.

Receptors of substance P:

- Three G-protein coupled receptors (NK_1,NK_2, and NK_3) medication the actions of Substance P, neurokinin A, and neurokinin B.
- Substance P is the favoured ligand for the NK_1 receptor, which is major tachykinin receptor in the brain.

Pharmacological Actions:

The pharmacological actions of substance P are:

1. Pain: substance P transmits painful stimuli from periphery to the spinal cord and higher brain structures. It controls dopamine release in striatal neurons. It is involved in anxiety, depression, emesis and nausea.
2. Cardiovascular System: Substance P causes vasodilation and hypotension by releasing nitric oxide from the endothelium.
3. Smooth Muscle: Substance P causes contraction of intestinal, venous and branchial smooth muscle.
4. Kidney: Substance P causes diuresis and natriuresis.

Therapeutic Uses:

- Both substance P and n eurokinin A are involved in neurogenic inflammation.
- It causes smooth muscle contraction acting on mast cells which release histamine.
- Causes delayed phase of asthma, inflammatory bowel disease and allergic rhinitis, etc.

Substance P Antagonist:

- Aprepitant is a NK_1 receptor antagonist which is orally administered.
- It has antiemetic effects in delayed nausea.
- It improves efficiency of standard antiemetic treatments in patients receiving multiple cycles of chemotherapy.
- More than 95% of aprepitant gets bound to plasma proteins.
- Metabolized by hepatic CYP3A4 which causes high dugs interactions.
- Aprepitant should not be administered with cisapride.
- Its half life is 9-13 hours and it gets excreted in stools.

Non-steroidal anti-inflammatory agents

Introduction

- Non-Steroidal Anti-Inflammatory Agents (NSAIDs) are a widely used class of medications known for their analgesic (pain-relieving), antipyretic (fever-reducing), and anti-inflammatory properties.
- They are commonly prescribed for conditions such as arthritis, musculoskeletal pain, migraines, dysmenorrhea, and postoperative pain. Unlike corticosteroids, NSAIDs do not suppress the adrenal axis and have a more favorable side effect profile for short-term use.
- Their global popularity stems from their effectiveness in managing mild to moderate pain and inflammation without the risk of addiction associated with opioids.

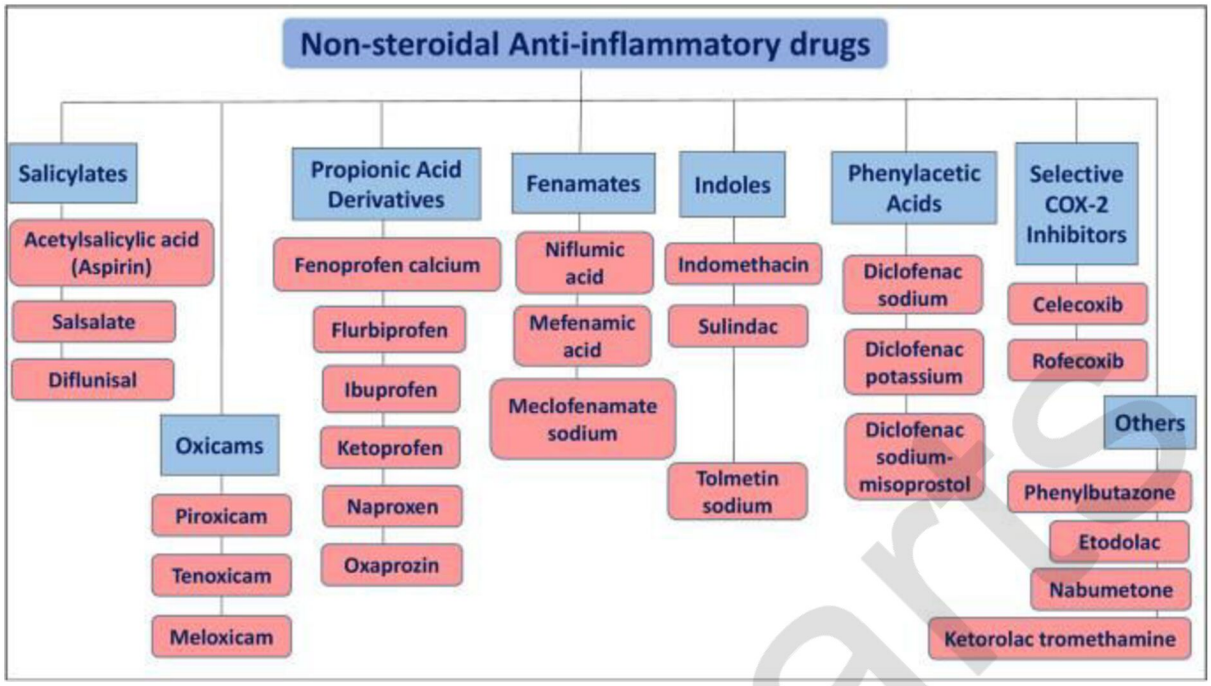
Mechanism of Action:

- NSAIDs primarily work by inhibiting the **cyclooxygenase (COX)** enzymes, which play a central role in the production of **prostaglandins**.
- Prostaglandins are lipid compounds that promote inflammation, pain, and fever.

The COX enzyme has two main isoforms:

1. **COX-1 (Cyclooxygenase-1):** This enzyme is constitutively expressed in most tissues and is involved in the production of prostaglandins that protect the stomach lining, support platelet function, and maintain kidney function.
2. **COX-2 (Cyclooxygenase-2):** This enzyme is induced during inflammation and is responsible for the production of prostaglandins that contribute to inflammation, pain, and fever.

Classification:



Aspirin:

- Also known as Acetyl salicylic acid.
- It is a protype drugs.
- It firstly converted into salicylic acid in the body then it gives there action.

MOA:

- It inhibits the enzyme cox.
- Which further decrease the production of inflammatory mediators such as PGs.
- Due to the decrease inflammatory response such as pain, fever etc.

Pharmacological Action:

- Acetylsalicylic acid has both anti-inflammatory and antipyretic effects.
- This drug also inhibits platelet aggregation and is used in the prevention of blood clots stroke, and myocardial infarction (MI) Label.
- GIT:
  - Irritate gastric mucosa and cause peptic ulcer.
  - Increase the risk of GI bleeding.
  - Cause Nausea, Vomiting.
- Blood: Anti-platelets effect by inhibiting TXA_2.

Uses:

- Aspirin is used to reduce fever and to relieve mild to moderate pain from headaches, menstrual periods, arthritis, toothaches, and muscle aches.

Anti-Gout Drugs

Introduction: Anti-gout drugs are medications used to treat gout, a form of arthritis caused by the accumulation of uric acid crystals in the joints, leading to inflammation and pain. Gout commonly affects the big toe but can also impact other joints.

Mechanism of Action: Anti-gout drugs are used to manage gout, a condition characterized by the deposition of uric acid crystals in the joints, leading to inflammation. These drugs work by either decreasing uric acid production, increasing its excretion, or reducing the inflammation caused by uric acid crystals.

Classification and Examples:

1. **Urate-Lowering Agents:**
    - **Allopurinol**: Inhibits **xanthine oxidase**, the enzyme responsible for converting hypoxanthine to xanthine and xanthine to uric acid, thus reducing uric acid production.
    - **Febuxostat**: Also inhibits **xanthine oxidase**, reducing the formation of uric acid.
2. **Uricosuric Agents:**
    - **Probenecid**: Promotes the renal excretion of uric acid by inhibiting its reabsorption in the kidneys.
3. **Anti-Inflammatory Drugs:**
    - **Colchicine**: Reduces inflammation by preventing neutrophil activation and migration to the site of uric acid crystal deposition.
    - **NSAIDs (e.g., Indomethacin, Ibuprofen)**: Provide symptomatic relief during acute attacks by reducing pain and inflammation.

Uses:

- Used for acute gout attacks.

- Long-term management to prevent future attacks by lowering uric acid levels (e.g., Allopurinol, Probenecid).
- Reducing inflammation during acute attacks (e.g., Colchicine, NSAIDs).

Antirheumatic Drugs

Introduction: Antirheumatic drugs are used in the treatment of autoimmune diseases like rheumatoid arthritis (RA), lupus, and other inflammatory conditions. These drugs aim to control the immune response, reduce inflammation, and prevent joint damage caused by these diseases.

Mechanism of Action: Antirheumatic drugs are used in the treatment of rheumatoid arthritis (RA) and other autoimmune diseases to reduce inflammation, suppress immune system activity, and slow disease progression. They work by modifying the immune response, inhibiting inflammatory cytokines, and altering the activity of the immune cells.

Classification and Examples:

1. **Disease-Modifying Antirheumatic Drugs (DMARDs):**
    - **Methotrexate**: A folate antagonist that inhibits dihydrofolate reductase, disrupting purine and pyrimidine synthesis and reducing immune cell proliferation.
    - **Leflunomide**: Inhibits **dihydroorotate dehydrogenase**, interfering with pyrimidine synthesis and inhibiting T-cell proliferation.
2. **Biologic DMARDs (TNF-α Inhibitors):**
    - **Etanercept**: A fusion protein that binds to TNF receptors, blocking the action of tumor necrosis factor (TNF-α), a key cytokine involved in RA inflammation.
    - **Adalimumab**: A monoclonal antibody that directly neutralizes TNF-α to decrease inflammation in autoimmune diseases.
3. **Janus Kinase (JAK) Inhibitors:**
    - **Tofacitinib**: Inhibits Janus kinases, which play a role in the signaling pathways of inflammatory cytokines, helping to reduce inflammation in RA.
4. **Non-Biologic DMARDs:**

- **Hydroxychloroquine**: An antimalarial drug that modulates immune function and inhibits antigen presentation, used mainly in RA and lupus.

5. **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):**
    - **Ibuprofen, Naproxen**: Provide relief from pain and inflammation but do not modify the disease progression.

Uses:

- **DMARDs** (Methotrexate, Leflunomide) are used to modify disease progression in RA and other autoimmune conditions.
- **Biologic DMARDs** (Etanercept, Adalimumab) are used when traditional DMARDs fail, targeting specific cytokines like TNF-α.
- **JAK inhibitors** (Tofacitinib) are used for moderate to severe RA that is resistant to conventional treatments.
- **NSAIDs** (Ibuprofen, Naproxen) are used for symptomatic relief of inflammation and pain in RA and other conditions.