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PHARMACOLOGY - II

UNIT 3

TOPIC :

- **Autocoids and related drugs**
 - a. Introduction to autocoids and classification
 - b. Histamine, 5-HT and their antagonists.
 - c. Prostaglandins, Thromboxanes and Leukotrienes.
 - d. Angiotensin, Bradykinin and Substance P.
 - e. Non-steroidal anti-inflammatory agents
 - f. Anti-gout drugs
 - g. Antirheumatic drugs

Autacoids

Autacoids are locally acting biologically active substances synthesized by cells and tissues that modulate physiological functions near their site of formation. They act autonomously to maintain homeostasis and respond to injury or stress.

Etymology:

The term “autacid” is derived from Greek:

- “autos” = self
- “akos” = remedy

Thus, autacoids are “self-remedies” that the body produces to regulate its own functions.

General Characteristics of Autacoids

1. Local Action: Act primarily near their site of synthesis; minimal systemic distribution under normal conditions.
2. Rapid Onset and Short Duration: Quickly synthesized and metabolized, producing transient effects.
3. Diverse Physiological Roles: Regulate vascular tone, smooth muscle activity, inflammation, neurotransmission, and hemostasis.
4. Produced on Demand: Many are synthesized in response to physiological or pathological stimuli.
5. Targets: Often act through specific cell surface receptors.
6. Examples: Histamine, serotonin (5-HT), bradykinin, prostaglandins, leukotrienes, nitric oxide.

Sources of Autacoids

Autacoid	Primary Source	Major Function
Histamine	Mast cells, basophils, gastric mucosa	Inflammation, gastric acid secretion, vasodilation
Serotonin (5-HT)	Platelets, enterochromaffin cells, CNS neurons	Vasoconstriction, platelet aggregation, neurotransmission
Bradykinin	Plasma (kininogen)	Vasodilation, pain, inflammation
Prostaglandins & Leukotrienes	Leukocytes, platelets, endothelial cells	Inflammation, smooth muscle contraction, platelet function
Nitric oxide	Endothelial cells, macrophages	Vasodilation, inhibition of platelet aggregation
Platelet-activating	Leukocytes, platelets	Inflammation, platelet activation

Classification of Autacoids

Autacoids can be classified based on chemical structure and pharmacological activity:

A. Biogenic Amines

- **Histamine**
 - **Source:** Mast cells, basophils, gastric mucosa, CNS
 - **Receptors:** H₁, H₂, H₃, H₄
 - **Actions:**
 - H₁ → smooth muscle contraction, vasodilation, bronchoconstriction
 - H₂ → gastric acid secretion, vasodilation
 - H₃ → autoreceptors in CNS → modulate neurotransmitter release
 - H₄ → chemotaxis of immune cells
- **Serotonin (5-HT)**
 - **Source:** Platelets, enterochromaffin cells, CNS
 - **Receptors:** 5-HT₁₋₇ subtypes
 - **Actions:** Vasoconstriction, platelet aggregation, GI motility, mood regulation

B. Peptides

- **Bradykinin**
 - **Source:** Plasma kininogen
 - **Actions:** Vasodilation, increased vascular permeability, pain
- **Angiotensin II**
 - **Source:** Liver → Renin-angiotensin system
 - **Actions:** Vasoconstriction, aldosterone release → sodium & water retention
- **Vasopressin (ADH)**

- **Source:** Hypothalamus → Posterior pituitary
- **Actions:** Water reabsorption in kidneys, vasoconstriction

C. Eicosanoids

- **Prostaglandins (PGs)**
 - Derived from arachidonic acid via cyclooxygenase (COX) pathway
 - **Functions:** Inflammation, pain, fever, vasodilation/constriction, platelet aggregation
- **Thromboxanes (TXA₂)**
 - **Source:** Platelets
 - **Actions:** Platelet aggregation, vasoconstriction
- **Prostacyclin (PGI₂)**
 - **Source:** Endothelium
 - **Actions:** Vasodilation, inhibits platelet aggregation
- **Leukotrienes (LTs)**
 - Derived via lipoxygenase pathway
 - **Actions:** Bronchoconstriction, increased vascular permeability, chemotaxis

D. Nitric Oxide (NO)

- **Source:** Endothelial cells, neurons, macrophages
- **Mechanism:** Activates guanylyl cyclase → ↑ cGMP → smooth muscle relaxation
- **Actions:** Vasodilation, inhibition of platelet aggregation, neurotransmission

E. Miscellaneous

- **Platelet-activating factor (PAF)**
 - **Source:** Leukocytes, platelets
 - **Actions:** Platelet aggregation, inflammation, bronchoconstriction
- **Adenosine**
 - **Source:** ATP metabolism

- **Actions:** Vasodilation, myocardial oxygen consumption reduction, antiarrhythmic effect

Histamine, 5-HT (Serotonin) and Their Antagonists

- Biogenic amines like histamine and serotonin (5-HT) are endogenous signaling molecules that regulate various physiological processes such as allergic responses, gastric acid secretion, neurotransmission, and vascular tone.
- Antagonists of these amines are important therapeutic agents for conditions like allergies, peptic ulcers, migraines, and serotonin-related disorders.

Part A – Histamine

Structure and Chemistry

- Histamine: 2-(imidazol-4-yl)ethylamine
- Derived from L-histidine by decarboxylation via histidine decarboxylase.

Sites of Storage

- Mast cells and basophils → allergies and inflammation
- Gastric enterochromaffin-like (ECL) cells → gastric acid secretion
- Brain neurons → neurotransmission

Histamine Receptors

Histamine acts via four receptor types (H_1 – H_4), all G-protein-coupled:

Receptor	Location	Signal Mechanism	Main Action / Effects
H_1	Smooth muscle, endothelium, CNS	$G_q \rightarrow PLC \rightarrow IP_3/DAG \rightarrow \uparrow Ca^{2+}$	Vasodilation, $\uparrow$ vascular permeability, bronchoconstriction, pruritus, wakefulness
H_2	Gastric parietal cells, heart, CNS	$G_s \rightarrow \uparrow cAMP$	$\uparrow$ Gastric acid secretion, $\uparrow$ heart rate & contractility
H_3	CNS (presynaptic)	$G_i \rightarrow \downarrow cAMP$	Autoreceptor: $\downarrow$ histamine release, modulates



			neurotransmission
H ₄	Hematopoietic cells, leukocytes	Gi → ↓ cAMP	Chemotaxis, inflammation, immune modulation

Pharmacological Actions of Histamine

System	Action
Cardiovascular	Vasodilation → ↓ BP; ↑ capillary permeability → edema; reflex tachycardia
Respiratory	Bronchoconstriction; ↑ mucus secretion
Gastrointestinal	↑ gastric acid secretion (H ₂)
CNS	Wakefulness, feeding behavior, thermoregulation
Immune system	Chemotaxis of eosinophils and neutrophils; mediator of allergic reactions

Histamine Antagonists

A. H₁ Receptor Antagonists

Examples: Diphenhydramine, Chlorpheniramine, Loratadine, Cetirizine

Mechanism:

Block H₁ → ↓ allergy symptoms (vasodilation, edema, bronchoconstriction, pruritus)

Uses:

- Allergic rhinitis, urticaria, anaphylaxis (as adjunct)
- Motion sickness and nausea (first-generation)
- Insomnia (sedative H₁ blockers)

Adverse Effects:

- Sedation (first-generation)

B. H₂ Receptor Antagonists

Examples: Ranitidine, Famotidine, Nizatidine, Cimetidine

Mechanism:

Block H₂ receptors on gastric parietal cells → ↓ gastric acid secretion

Uses:

- Peptic ulcer disease
- Gastroesophageal reflux disease (GERD)

- Zollinger-Ellison syndrome

Adverse Effects:

- Headache, diarrhea
- Cimetidine: gynecomastia, drug interactions (CYP₄₅₀ inhibitor)

C. H₃ Receptor Antagonists

Examples: Pitolisant (used in narcolepsy)

Mechanism: Block presynaptic H₃ → ↑ histamine release in CNS → wakefulness

Uses:

- Narcolepsy, excessive daytime sleepiness

Adverse Effects:

- Insomnia, headache, nausea

D. H₄ Receptor Antagonists

Experimental / clinical trials:

- JNJ-7777120, Adriformant

Uses:

- Inflammatory diseases, pruritus, asthma

Part B – 5-HT (Serotonin)

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter involved in:

- Mood regulation, sleep, appetite
- GI motility and secretion
- Vasoconstriction and platelet aggregation

Biosynthesis:

- L-tryptophan → 5-hydroxytryptophan → 5-HT (via tryptophan hydroxylase & decarboxylase)

Storage:

- Platelets → release in clotting
- Enterochromaffin cells → GI regulation
- CNS neurons → neurotransmission

5-HT Receptors

- All G-protein-coupled, except 5-HT₃ (ligand-gated cation channel)
- Classified as 5-HT₁ to 5-HT₇

Receptor	Location	Action / Mechanism	Clinical Relevance
5-HT ₁ (A/B/D)	CNS, blood vessels	Gi → ↓ cAMP	Migraine (5-HT _{1D} agonist), anxiety
5-HT ₂ (A/B/C)	CNS, smooth muscle, platelets	Gq → ↑ IP ₃ /DAG → ↑ Ca ²⁺	Vasoconstriction, platelet aggregation, smooth muscle contraction
5-HT ₃	CNS (CTZ), GI tract	Ligand-gated Na ⁺ /K ⁺ channel	Nausea, vomiting → target for antiemetics
5-HT ₄	GI tract	Gs → ↑ cAMP	↑ GI motility (prokinetic drugs)
5-HT ₇	CNS, smooth muscle	Gs → ↑ cAMP	Circadian rhythm, vasodilation

Pharmacological Actions of Serotonin

System	Action
CNS	Mood regulation, sleep, appetite
GI	↑ peristalsis, secretion from enterochromaffin cells
Cardiovascular	Vasoconstriction (via 5-HT ₂) or vasodilation (5-HT ₁ /5-HT ₇ depending on vessel)
Platelets	Aggregation via 5-HT _{2A}

5-HT Antagonists

A. 5-HT₃ Receptor Antagonists

Examples: Ondansetron, Granisetron, Palonosetron

Mechanism: Block 5-HT₃ receptors → inhibit vomiting reflex in CNS and GI tract

Uses:

- Chemotherapy-induced nausea and vomiting (CINV)
- Postoperative nausea and vomiting

Adverse Effects:

- Headache, constipation, QT prolongation

B. 5-HT₂ Receptor Antagonists

Examples: Ketanserin, Ritanserin

Mechanism: Block 5-HT₂ → ↓ vasoconstriction, platelet aggregation

Uses:

- Hypertension (Ketanserin)
- Experimental: psychiatric disorders, migraine

C. 5-HT₁ Agonists (Triptans)

Examples: Sumatriptan, Rizatriptan

Mechanism: 5-HT_{1B/1D} agonists → cranial vasoconstriction, ↓ neuropeptide release

Uses: Acute migraine attacks

D. 5-HT₄ Agonists (Prokinetics)

Examples: Cisapride, Prucalopride

Mechanism: Stimulate GI motility → enhance peristalsis

Uses: Constipation, gastroparesis

E. Others

- SSRIs (Fluoxetine, Sertraline): Indirect 5-HT agonist by inhibiting reuptake → depression, anxiety
- SNRIs: ↑ serotonin & norepinephrine → depression, neuropathic pain

Prostaglandins (PGs)

- Prostaglandins are a group of physiologically active lipid compounds derived from arachidonic acid.
- They belong to the class of eicosanoids and are produced in almost all tissues.
- They act as local hormones (autocrine and paracrine), mediating inflammation, pain, fever, vascular tone, and smooth muscle activity.

Historical note: Named after the prostate gland, where they were first discovered, though they are produced in many tissues.

Biosynthesis

1. Precursor: Arachidonic acid (from membrane phospholipids via phospholipase A₂)
2. Enzymes involved: Cyclooxygenase (COX-1 and COX-2)
3. Pathway:
 - Arachidonic acid → PGG₂ → PGH₂ (via COX)
 - PGH₂ is then converted to various prostaglandins and thromboxanes by specific synthases

Key enzymes:

- COX-1: Constitutive, housekeeping roles (gastric protection, platelet function)
- COX-2: Inducible, upregulated during inflammation and pain

Major Types of Prostaglandins

Prostaglandin	Primary Site / Source	Main Action
PGE ₁ (Alprostadil)	Vascular smooth muscle, reproductive system	Vasodilation, maintain ductus arteriosus, inhibit platelet aggregation
PGE ₂ (Dinoprostone)	Uterus, kidney, GI tract	Uterine contraction, cervical ripening, fever, vasodilation
PGF ₂ α (Carboprost)	Uterus, eye, lungs	Uterine contraction, bronchoconstriction, ocular pressure regulation
PGD ₂	Mast cells, CNS	Vasodilation, bronchoconstriction, sleep regulation
PGI ₂ (Prostacyclin,	Endothelial cells	Vasodilation, inhibit platelet

Epoprostenol)	aggregation, renal protection
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Pharmacological Actions of Prostaglandins

System / Organ	Action
Cardiovascular	PGE ₁ , PGI ₂ : Vasodilation, ↓ platelet aggregation; PGF ₂ α: vasoconstriction in some vascular beds
Gastrointestinal	PGE ₂ , PGI ₂ : ↑ mucus & bicarbonate secretion, ↓ acid secretion (protect gastric mucosa)
Renal	↑ renal blood flow, ↑ Na ⁺ and water excretion
Reproductive	PGF ₂ α, PGE ₂ : Uterine contraction, cervical ripening, induction of labor
Respiratory	PGF ₂ α, PGD ₂ : Bronchoconstriction, airway regulation
CNS	PGD ₂ : Sleep regulation; PGE ₂ : Fever induction via hypothalamus

Clinical Uses of Prostaglandins

Prostaglandin / Analogue	Therapeutic Use
Alprostadil (PGE ₁)	Maintain patent ductus arteriosus in neonates; erectile dysfunction
Misoprostol (PGE ₁ analogue)	Prevent NSAID-induced gastric ulcers; induce labor/abortion
Dinoprostone (PGE ₂)	Cervical ripening; induction of labor
Carboprost (PGF ₂ α)	Control postpartum hemorrhage; abortion induction
Epoprostenol / Iloprost (PGI ₂ analogues)	Pulmonary arterial hypertension; inhibit platelet aggregation

Adverse Effects

- Diarrhea, abdominal cramps (PGE analogues)
- Fever (PGE₂)
- Hypotension (PGE₁, PGI₂)
- Bronchoconstriction (PGF₂α)

- Uterine hyperstimulation → risk of fetal distress during labor induction

THROMBOXANES (TXs)

- Thromboxanes are eicosanoids derived from arachidonic acid via the cyclooxygenase (COX) pathway.
- They are primarily produced by platelets and are key mediators of platelet aggregation and vasoconstriction.
- Thromboxanes play an important role in hemostasis and thrombosis.

Biosynthesis

1. Arachidonic acid (from membrane phospholipids) → PGG_2 → PGH_2 via COX-1 or COX-2
2. PGH_2 → TXA_2 (Thromboxane A_2) via thromboxane synthase in platelets
3. TXA_2 is unstable → rapidly converted to inactive TXB_2

Key points:

- TXA_2 : active form, promotes platelet aggregation and vasoconstriction
- TXB_2 : inactive metabolite, used as a biomarker of TXA_2 synthesis

Types of Thromboxanes

- TXA_2 (Thromboxane A_2): Main biologically active thromboxane
- TXB_2 : Inactive metabolite, measured in urine or plasma
- TXA_3 : Minor form (from EPA, omega-3), less active

Pharmacological Actions of Thromboxanes

System / Organ	Action
Platelets	Promotes platelet aggregation → formation of thrombus
Vascular	Vasoconstriction → ↑ blood pressure, reduces blood flow in microcirculation

Smooth Muscle	Contraction in uterus and lungs
Renal	Modulate glomerular filtration and renal blood flow (minor)

Clinical Significance

A. Therapeutic Targeting

- Aspirin (low-dose): Irreversibly inhibits COX-1 → ↓ TXA₂ synthesis → antiplatelet effect
- Thromboxane receptor antagonists: Experimental use in cardiovascular disorders
- Omega-3 fatty acids: Lead to TXA₃ → reduced platelet aggregation

B. Pathophysiology

- Excess TXA₂: Promotes thrombosis, atherosclerosis, myocardial infarction, and stroke
- Deficient TXA₂: Leads to bleeding tendency (rare platelet function disorders)

Drugs Affecting Thromboxanes

Drug / Class	Mechanism	Clinical Use
Aspirin (low-dose)	Irreversible COX-1 inhibition → ↓ TXA ₂	Prevention of MI, stroke, arterial thrombosis
Thromboxane receptor antagonists	Block TXA ₂ receptor (TP receptor)	Experimental: anti-thrombotic therapy
Omega-3 fatty acids	Reduce TXA ₂ formation, promote TXA ₃	Cardiovascular protection

LEUKOTRIENES (LTs)

- Leukotrienes are biologically active lipid mediators derived from arachidonic acid via the 5-lipoxygenase (5-LOX) pathway.
- They are mainly produced by leukocytes (neutrophils, eosinophils, mast cells, macrophages).
- Leukotrienes are potent mediators of inflammation, bronchoconstriction, and allergic reactions.
- They are classified as LTB₄ and cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄).

Biosynthesis

1. Arachidonic acid (AA) → 5-HPETE via 5-lipoxygenase (5-LOX)
2. 5-HPETE → Leukotriene A₄ (LTA₄)
3. LTA₄ →
 - LTB₄ (via LTA₄ hydrolase) → chemotactic and pro-inflammatory
 - LTC₄ (via LTC₄ synthase) → cysteinyl leukotrienes → LTD₄, LTE₄

Key points:

- Leukotrienes act locally at site of production
- Their actions are mediated by specific G-protein-coupled receptors (BLT_{1/2} for LTB₄, CysLT_{1/2} for cysteinyl LTs)

Types and Functions

Leukotriene	Receptor / Action	Physiological / Pathophysiological Effect
LTB ₄	BLT ₁ /BLT ₂	Chemotaxis of neutrophils, inflammation, tissue injury
LTC ₄ , LTD ₄ , LTE ₄	CysLT ₁ / CysLT ₂	Bronchoconstriction, ↑ vascular permeability, mucus secretion, edema
LTF ₄	CysLT receptors	Bronchoconstriction, inflammatory response

Pharmacological Actions

System / Organ	Action
Respiratory	CysLTs → bronchoconstriction, airway edema, increased mucus secretion
Immune / Inflammation	LTB ₄ → neutrophil chemotaxis, promotes inflammation
Vascular	↑ vascular permeability → tissue edema
Gastrointestinal	Modulates smooth muscle contraction in some cases

Clinical Relevance

A. Therapeutic Targets

- Asthma and allergic rhinitis: Overproduction of cysteinyl LTs → bronchospasm and airway inflammation
- Anti-leukotriene drugs: Block LT synthesis or receptor activation

B. Drugs Acting on Leukotrienes

Drug / Class	Mechanism	Clinical Use
Montelukast, Zafirlukast	CysLT ₁ receptor antagonists	Asthma, allergic rhinitis, exercise-induced bronchoconstriction
Zileuton	5-LOX inhibitor → ↓ LT synthesis	Asthma
Pranlukast	CysLT ₁ antagonist	Asthma, seasonal allergies

Pathophysiological Role

- Asthma: CysLTs → bronchoconstriction, mucus hypersecretion, airway edema
- Allergic rhinitis: LT-mediated nasal congestion and inflammation
- Inflammation / Chemotaxis: LTB₄ recruits neutrophils → tissue damage
- Cardiovascular disease: Leukotrienes may contribute to atherosclerosis and vascular inflammation

ANGIOTENSIN

- Angiotensin is a peptide hormone that plays a central role in regulation of blood pressure, fluid, and electrolyte balance.
- It is part of the Renin-Angiotensin-Aldosterone System (RAAS), which maintains vascular tone, sodium, and water homeostasis.

Key Points:

- Angiotensin itself is biologically inactive initially and is converted to active forms by specific enzymes.
- Angiotensin has multiple isoforms with distinct physiological roles.

Biosynthesis of Angiotensin

1. Renin release:

- Secreted by juxtaglomerular cells of kidney in response to:
 - ↓ Blood pressure
 - ↓ Sodium in distal tubules
 - Sympathetic stimulation (β_1 receptors)

2. Stepwise conversion:

Step	Enzyme	Product	Comments
Angiotensinogen (from liver) → Angiotensin I	Renin	Angiotensin I	Inactive decapeptide
Angiotensin I → Angiotensin II	ACE (Angiotensin-Converting Enzyme, mainly lungs)	Angiotensin II	Active octapeptide; major vasoconstrictor
Angiotensin II → Angiotensin III	Aminopeptidase	Angiotensin III	Retains aldosterone-stimulating activity
Angiotensin II → Angiotensin (1-7)	ACE2	Angiotensin (1-7)	Vasodilatory, counter-regulatory effect

Types of Angiotensin Receptors

Receptor	Location	Function / Action
AT ₁	Vascular smooth muscle, kidney, adrenal cortex, heart, brain	Vasoconstriction, aldosterone release, sodium retention, sympathetic activation
AT ₂	Fetal tissue, some adult tissues	Vasodilation, anti-proliferative, natriuresis, tissue repair
Mas receptor	Blood vessels, heart, kidney	Mediates effects of Angiotensin (1-7): vasodilation, anti-fibrotic, anti-proliferative

Physiological Actions of Angiotensin II

System / Organ	Action
Cardiovascular	Potent vasoconstriction → ↑ blood pressure
Kidneys	↑ Sodium and water reabsorption (proximal tubule) → ↑ blood volume
Adrenal Cortex	Stimulates aldosterone secretion → ↑ Na ⁺ retention, K ⁺ excretion
Sympathetic Nervous System	↑ NE release → ↑ heart rate & contractility
Heart & Vessels	Stimulates hypertrophy and remodeling
CNS	Stimulates thirst → ↑ water intake; ↑ ADH release

Pathophysiological Role

- Hypertension: ↑ RAAS activity → chronic vasoconstriction and volume overload
- Heart failure: Angiotensin II → cardiac remodeling and fibrosis
- Kidney disease: ↑ intraglomerular pressure → proteinuria, progression of CKD
- Edema formation: Via sodium and water retention

BRADYKININ

- Bradykinin is a potent endogenous peptide of the kinin–kallikrein system.
- It is a nonapeptide (9 amino acids) produced from kininogen by the enzyme kallikrein.
- Plays a major role in vasodilation, vascular permeability, inflammation, pain, and smooth muscle contraction.
- Short-lived due to rapid degradation by kininases (including ACE).

Biosynthesis

1. High molecular weight kininogen (HMWK) → Bradykinin via plasma kallikrein
2. Low molecular weight kininogen (LMWK) → Lysyl-bradykinin (kallidin) via tissue kallikrein
3. Bradykinin is inactivated by:
 - Angiotensin-Converting Enzyme (ACE / kininase II)
 - Carboxypeptidases
 - Neutral endopeptidases

Bradykinin Receptors

Bradykinin acts via G-protein-coupled receptors:

Receptor	Location	Action
B ₁	Induced in inflamed tissues	Mediates pain, inflammation, cytokine release
B ₂	Constitutive (vascular endothelium, smooth muscle, kidney)	Vasodilation, vascular permeability, natriuresis, smooth muscle contraction

Pharmacological Actions of Bradykinin

System / Organ	Action
Cardiovascular	Vasodilation → ↓ blood pressure; stimulates release of NO, prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF)
Vascular Permeability	↑ permeability → edema formation
Pain & Inflammation	Direct nociceptor stimulation → pain; induces prostaglandin release → inflammation
Smooth Muscle	Contraction of bronchial, intestinal, and uterine smooth muscle
Renal	↑ renal blood flow, natriuresis, and diuresis via B ₂ receptors
Endocrine / Autacoids	Stimulates release of aldosterone, ADH, and other mediators

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SUBSTANCE P

- Substance P (SP) is an endogenous neuropeptide belonging to the tachykinin family.
- It acts as a neurotransmitter and neuromodulator in the central and peripheral nervous systems.
- Plays a key role in pain perception, inflammation, vasodilation, and smooth muscle contraction.
- First discovered in 1931, named for its ability to cause “powdered substance” activity in tissue extracts.

Structure and Distribution

- Structure: Undecapeptide (11 amino acids)
- Gene: Encoded by the TAC₁ gene in humans
- Distribution:
 - CNS: Spinal cord, basal ganglia, hypothalamus
 - PNS: Sensory neurons (dorsal root ganglia), enteric nervous system
 - Other tissues: Lungs, GI tract, cardiovascular system

Biosynthesis

1. Preprotachykinin gene transcription → Preprotachykinin A or B
2. Processing by peptidases → Substance P
3. Stored in vesicles of sensory neurons, released upon nociceptive or inflammatory stimulation

Receptors

- Neurokinin-1 receptor (NK₁R): Main receptor mediating SP effects
- Other receptors: NK₂R, NK₃R (less affinity)
- G-protein-coupled receptor (GPCR) → activates phospholipase C, IP₃, DAG, Ca²⁺ signaling

Pharmacological Actions

System / Organ	Action
Pain / CNS	Transmits pain signals from peripheral sensory neurons to CNS → nociception
Inflammation	↑ Vascular permeability, mast cell degranulation → edema, redness
Vasculature	Vasodilation via NO and prostaglandin release → ↓ blood pressure locally
Gastrointestinal	↑ smooth muscle contraction → peristalsis; ↑ secretion
Respiratory	Bronchoconstriction, mucus secretion
Immune System	Modulates cytokine release, chemotaxis of immune cells

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Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- NSAIDs are a group of drugs that reduce inflammation, pain, and fever without being steroids.
- They primarily act by inhibiting cyclooxygenase (COX) enzymes, thereby reducing prostaglandin synthesis.
- Clinical uses: Pain relief (analgesic), anti-inflammatory, antipyretic, and antiplatelet (in selected drugs).

Mechanism of Action

- Cyclooxygenase (COX) Inhibition:
Prostaglandins are synthesized from arachidonic acid by COX enzymes. NSAIDs block this pathway.

COX isoforms:

1. COX-1: Constitutive enzyme in stomach, platelets, kidneys; physiological prostaglandins → gastric protection, platelet aggregation, renal function.
 2. COX-2: Inducible enzyme during inflammation; produces prostaglandins responsible for pain, inflammation, and fever.
- Result: ↓ Prostaglandins → ↓ inflammation, pain, fever, and platelet aggregation (for some drugs).

Classification of NSAIDs

A. Salicylates

- Examples: Aspirin, Sodium salicylate, Diflunisal
- Key Features:
 - Irreversible COX inhibition.
 - Anti-inflammatory, analgesic, antipyretic.
 - Antiplatelet effect → prevention of myocardial infarction and stroke.

B. Para-Aminophenols

- Example: Paracetamol (Acetaminophen)
- Key Features:
 - Weak anti-inflammatory activity.
 - Analgesic and antipyretic.
 - Minimal gastric irritation; acts mainly in CNS.

C. Propionic Acid Derivatives

- Examples: Ibuprofen, Naproxen, Ketoprofen
- Key Features:
 - Non-selective COX inhibitors.
 - Anti-inflammatory, analgesic, antipyretic.
 - Safer on stomach than aspirin.

D. Acetic Acid Derivatives

- Examples: Indomethacin, Diclofenac, Ketorolac
- Key Features:
 - Strong anti-inflammatory activity.
 - Used in arthritis, gout, post-operative pain.
 - Higher risk of gastrointestinal side effects.

E. Oxicam (Enolic Acid) Derivatives

- Examples: Piroxicam, Meloxicam
- Key Features:
 - Long-acting NSAIDs.
 - Used in chronic inflammatory conditions like rheumatoid arthritis.

F. Fenamates

- Examples: Mefenamic acid, Tolfenamic acid
- Key Features:
 - Mild to moderate pain relief.
 - Anti-inflammatory; used for dysmenorrhea and musculoskeletal pain.

G. COX-2 Selective Inhibitors (Coxibs)

- Examples: Celecoxib, Etoricoxib
- Key Features:
 - Selectively inhibit COX-2 → anti-inflammatory and analgesic.
 - Reduced gastric irritation compared to non-selective NSAIDs.

H. Sulfonanilides

- Example: Nimesulide
- Key Features:
 - Preferential COX-2 inhibitor.

- Analgesic, anti-inflammatory.

Pharmacological Actions

1. Anti-inflammatory: Reduce edema, redness, and pain by inhibiting prostaglandins.
2. Analgesic: Relieve mild to moderate pain (headache, musculoskeletal, dysmenorrhea).
3. Antipyretic: Reduce fever by acting on the hypothalamic heat-regulating center.
4. Antiplatelet (mainly aspirin): Inhibits thromboxane A_2 → prevents platelet aggregation.

Clinical Uses

- Pain: Headache, toothache, arthritis, musculoskeletal pain.
- Inflammation: Rheumatoid arthritis, osteoarthritis, gout, bursitis.
- Fever: Paracetamol or aspirin in febrile conditions.
- Cardiovascular: Low-dose aspirin for prevention of myocardial infarction and stroke.
- Post-operative analgesia: Diclofenac, Ketorolac.
- Dysmenorrhea: Ibuprofen, Mefenamic acid.

Adverse Effects

1. Gastrointestinal: Gastric irritation, ulceration, bleeding.
2. Renal: Reduced renal blood flow, sodium and water retention, possible nephrotoxicity.
3. Cardiovascular: Increased risk of myocardial infarction and stroke (especially with COX-2 selective drugs).
4. Hematological: Platelet dysfunction, prolonged bleeding time.
5. Hypersensitivity reactions: Rash, urticaria, asthma exacerbation.
6. Hepatic: Rare hepatotoxicity (e.g., Nimesulide).
7. Pregnancy: Avoid in 3rd trimester due to premature closure of ductus arteriosus.

Anti-Gout Drugs

Anti-gout drugs are medications used to treat gout, a type of arthritis caused by the deposition of uric acid crystals (monosodium urate) in joints, leading to inflammation, pain, and swelling.

Objectives of Therapy:

1. Relieve acute attacks (pain and inflammation).
2. Prevent recurrence of attacks.
3. Reduce serum uric acid levels to prevent urate crystal deposition.

Mechanism of Gout Pathophysiology:

- Overproduction of uric acid or decreased excretion → hyperuricemia → urate crystal deposition → inflammation.
- Treatment aims to reduce inflammation and/or lower uric acid levels.

Classification of Anti-Gout Drugs

A. Drugs for Acute Gout Attack

These drugs relieve pain and inflammation during an acute attack.

1. NSAIDs

- Used to reduce pain and inflammation in acute gout.
- Examples: Indomethacin, Naproxen, Diclofenac.
- Key Points:
 - First-line therapy for acute attacks.
 - Rapid onset, effective in reducing joint pain.
 - Avoid in renal impairment or peptic ulcer patients.

2. Colchicine

- Source: Alkaloid from *Colchicum autumnale*.
- Mechanism:
 - Inhibits microtubule polymerization → prevents neutrophil migration and phagocytosis of urate crystals → reduces inflammation.
- Uses: Acute gout attacks, prophylaxis of recurrent attacks.
- Adverse Effects: GI upset (diarrhea, nausea), myopathy, bone marrow suppression at high doses.
- Dosage: Typically 1–1.2 mg at onset, then 0.5–0.6 mg every 2–3 hours until pain relief or toxicity.

3. Corticosteroids

- Examples: Prednisolone, Methylprednisolone.
- Mechanism: Anti-inflammatory and immunosuppressive effects.
- Uses: For patients intolerant to NSAIDs or colchicine.
- Route: Oral, intra-articular, or parenteral.

B. Drugs for Chronic Gout (Urate-Lowering Therapy)

Used to reduce serum uric acid levels and prevent recurrent attacks.

1. Xanthine Oxidase Inhibitors (XOIs)

- Mechanism: Inhibit xanthine oxidase, the enzyme converting hypoxanthine → xanthine → uric acid, thus reducing uric acid production.
- Examples: Allopurinol, Febuxostat, Topiroxostat.
- Key Points:
 - First-line therapy for chronic gout.
 - May precipitate acute attack initially → often co-administered with colchicine.

- Febuxostat: Selective XO inhibitor, safer in mild renal impairment.

2. Uricosuric Agents

- Mechanism: Increase renal excretion of uric acid by inhibiting reabsorption in proximal tubules.
- Examples: Probenecid, Benzbromarone, Sulfapyrazone.
- Key Points:
 - Useful in under-excretors of uric acid.
 - Avoid in patients with renal stones or renal impairment.
 - Can increase risk of uric acid nephrolithiasis.

3. Recombinant Uricases

- Mechanism: Converts uric acid into soluble allantoin, which is easily excreted.
- Examples: Pegloticase, Rasburicase.
- Uses: Severe refractory gout not responding to other therapy.
- Adverse Effects: Hypersensitivity reactions, infusion reactions.

4. Other Drugs

- Losartan (angiotensin receptor blocker): Mild uricosuric effect, sometimes useful in hypertensive gout patients.
- Fenofibrate: Mild uricosuric effect, occasionally used in gout with hyperlipidemia.

Antirheumatic Drugs

- Rheumatic diseases include a broad group of disorders affecting joints, muscles, and connective tissue, such as rheumatoid arthritis (RA), osteoarthritis (OA), and systemic lupus erythematosus (SLE).
- Antirheumatic drugs are medications used to reduce inflammation, relieve pain, and slow disease progression in these disorders.

Classification of Antirheumatic Drugs

Antirheumatic drugs are broadly classified into:

A. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Examples: Ibuprofen, Naproxen, Diclofenac, Indomethacin
- Mechanism: Inhibit cyclooxygenase (COX-1 & COX-2) → ↓ prostaglandin synthesis → analgesic, anti-inflammatory, antipyretic effects.
- Uses: Pain and inflammation relief in RA, OA, and other rheumatic disorders.
- Adverse effects: GI irritation, renal impairment, bleeding, hypersensitivity reactions.

B. Disease-Modifying Antirheumatic Drugs (DMARDs)

- Purpose: Slow or halt disease progression in autoimmune rheumatic diseases, especially RA.
- Types:
 1. Conventional Synthetic DMARDs (csDMARDs)
 - Methotrexate: Folate antagonist; inhibits DNA synthesis → immunosuppressive → first-line in RA.
 - Sulfasalazine: Anti-inflammatory and immunomodulatory; used in RA and ankylosing spondylitis.

- Leflunomide: Inhibits pyrimidine synthesis → reduces T-cell proliferation.
- Hydroxychloroquine: Antimalarial; immunomodulatory; mild RA.
- 2. Biologic DMARDs (bDMARDs)
 - Tumor Necrosis Factor (TNF) inhibitors: Etanercept, Infliximab, Adalimumab → block TNF- α → reduce inflammation.
 - IL-6 receptor antagonists: Tocilizumab → inhibits IL-6 mediated inflammation.
 - B-cell depletion: Rituximab → targets CD20+ B cells.
- 3. Targeted Synthetic DMARDs (tsDMARDs)
 - JAK inhibitors: Tofacitinib, Baricitinib → inhibit Janus kinase signaling → reduce immune-mediated inflammation.
- Adverse effects of DMARDs: Immunosuppression, infections, liver toxicity, cytopenias, gastrointestinal upset.

C. Corticosteroids

- Examples: Prednisolone, Methylprednisolone, Dexamethasone
- Mechanism: Bind to glucocorticoid receptors → inhibit cytokine production and inflammatory gene expression.
- Uses: Short-term control of inflammation in RA, lupus flares, vasculitis.
- Adverse effects: Osteoporosis, hyperglycemia, adrenal suppression, weight gain, hypertension.

D. Analgesics / Adjunctive Therapy

- Acetaminophen (Paracetamol): Pain relief in mild OA and RA without anti-inflammatory effect.
- Opioids (rarely): For severe pain unresponsive to other medications.