

The background features a dark blue gradient with a subtle pattern of white dots. Overlaid on this are several faint, light-colored circular diagrams. A prominent diagram on the left is a large circle with a scale around its perimeter, ranging from 140 to 260 in increments of 10. Inside this circle are smaller concentric circles and dashed lines, some with arrows indicating direction. Other similar but smaller diagrams are scattered across the background.

AUTACOIDS

SHIVV

INTRODUCTION:

- AUTACOIDS auto=self akos=healing/remedy
- These are diverse substances produced by a *wide variety of cells in the body, having intense biological activity, but generally act locally (e.g. within inflammatory pockets) at the site of synthesis and release.*
- They have also been called 'local hormones'

CLASSIFICATION:

- **Amine derived:**
 - Histamine (amino acid: Histidine), Serotonin (Tryptophan)
- **Peptide derived:**
 - Angiotensin, Bradykinin
- **Lipid derived:**
 - Prostaglandins, Leukotrienes, Interleukins, Platelet Activating Factor, etc.

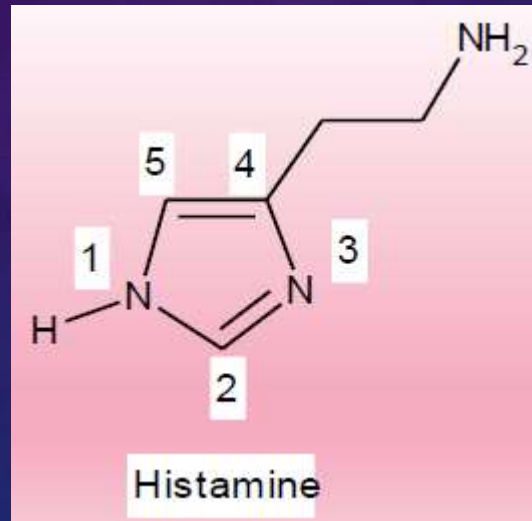
FUNCTIONS:

- Physiological
- Pathophysiological (Reaction to injuries)
- Transmission and Modulation

AMINE AUTACOIDS:

- DERIVED FROM NATURAL AMINO ACIDS
- HISTAMINE AND SEROTONIN are the major autacoids in this class

HISTAMINE:



INTRODUCTION:

- Imidazole ethylamine
- Formed from the amino acid *Histidine*
- Important inflammatory mediator
- Potent biogenic amine and plays an important role in inflammation, anaphylaxis, allergies, gastric acid secretion and drug reaction
- As part of an immune response to foreign pathogens, its produced by Basophils and mast cells found in nearby connective tissues.

SITES OF HISTAMINE RELEASE

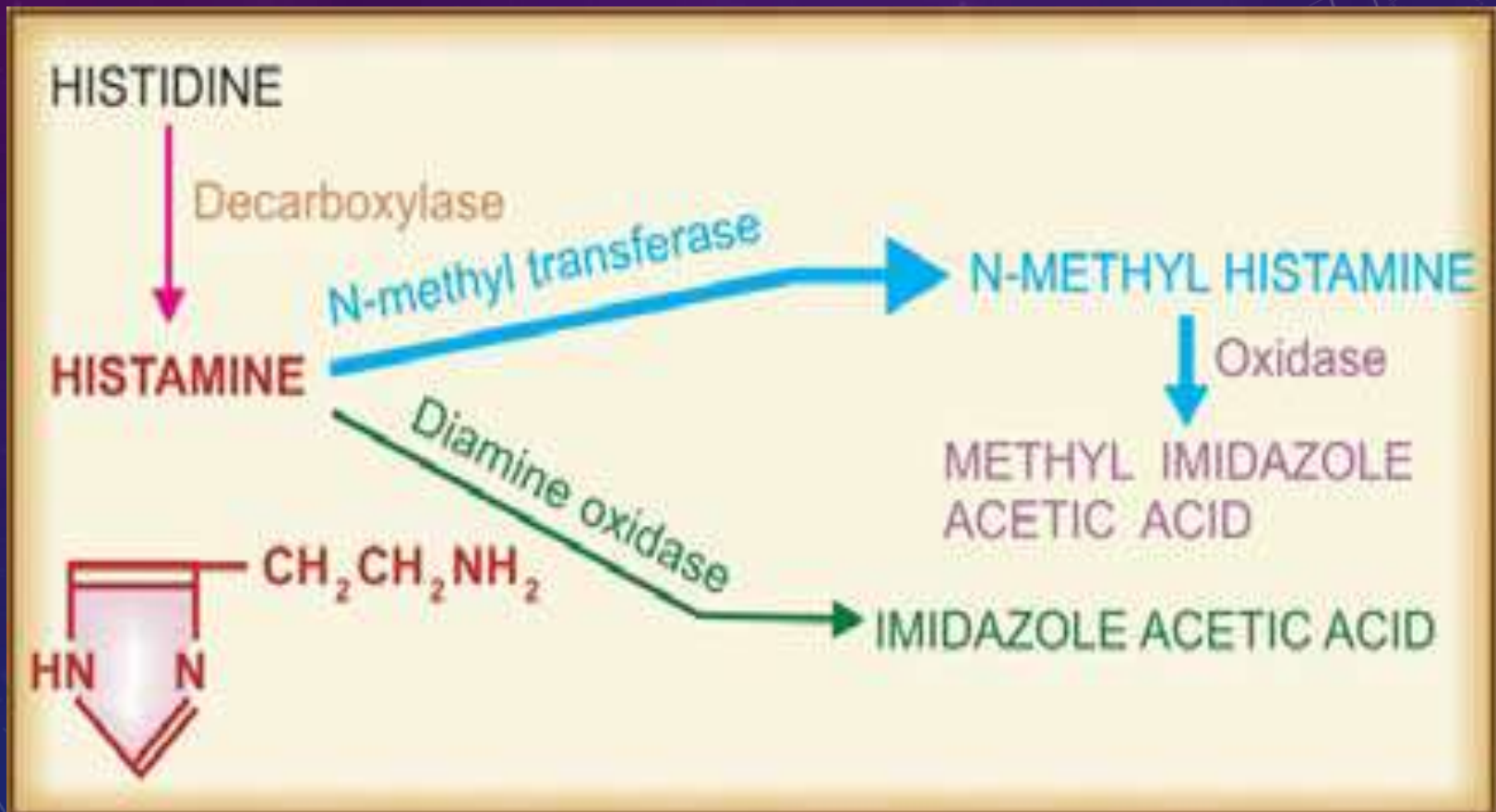
1) Mast cell site:

- Pulmonary tissue (mucosa of bronchial tree)
- Skin
- GIT(intestinal mucosa)
- Conc. Of histamine is particularly high in these tissues

2) Non-mast cell sites:

- CNS (neurons)
- Epidermis of skin.
- GIT(gastric cells)
- Cells in regenerating or rapidly growing tissues
- Basophils (in the blood)

SYNTHESIS AND DEGRADATION:



MECHANISM OF RELEASE:

- Histamine held by an acidic protein and heparin within intracellular granules → Granules extrude by exocytosis → Na^+ gets exchanged for histamine
- Substances released during IgG or IgM immunoreactions release histamine from the mast cells & basophil.
- Chemical & mechanical mast cells injury causes degranulation of cytoplasmic granules & histamine is released
- Certain amines accumulate in mast cells due to affinity for heparin, displace histamine → form heparin liberator complex → increases permeability of mast cell membrane and diffuse histamine.

receptor	mechanism	Location and function	agonists	antagonists
H 1	Gq type IP3/DAG : Release of Ca ²⁺ Pk-C activation	Smooth muscle (GIT, airway, uterus)- contraction blood vessels: Endothelium- VD Smooth muscle - VC brain – transmitter Adrenal – release of CAs.	2 methyl histamine, 2-pyridyl ethylamine,	Mepyramine, chlorphenara mine,
H 2	Gs type Increase in c AMP. Phosphorylati on of specific proteins	Gastric – acid secretion. Blood vessels (smooth muscle)- dilation. heart: A- +ve chrono and V - +ve ionotropy Brain - transmitter	4 methyl histamine, dimaprit, impromidone	Cimentidine, ranitidine
H 3	G i – autoreceptor. Dec in ca influx Dec in c AMP.	(presynaptic) – inhibition of release – sedation(brain), Ileum – dec in Ach release Blood vessels – dec in NA release - VD	(R) α methyl histamine, imetit	Thioperamind e, impromidine, ciproflaxacin
H 4	G I Dec in c AMP	Mediate mast cell chemotaxis		Thioperamide

TRIPLE RESPONSE:

- Intra dermal injection of histamine elicits triple response
- **Red spot at the site:**
 - Flush
 - Due to local capillary dilation.
- **Flare:**
 - Redness surrounding the flush due arteriolar dilatation.
- **Wheal:**
 - Local oedema due to escape of fluids from capillaries.

PATHOPHYSIOLOGICAL ROLES:

- ulcers: excessive stimulation of H₂ produces excess acid secretion.
- Allergic phenomenon: mediation of hypersensitivity reactions has been the first role ascribed to histamine.
 - Causes inflammation - chemotaxis, opsonisation (recognize antigens)
- Tissue growth and repair
- Headache – due to sudden vasodilatation produce headache.

USES:

- No therapeutic value
- Occasionally used in some diagnostic tests:
 - Testing gastric acid secretion.
 - Diagnosis of pheochromocytoma.
 - Pulmonary function: to test for bronchial hyper-reactivity.

HISTAMINE SUBSTITUTES

- Betahistine
 - H1 agonist
 - Used to control vertigo in patients of meniere's disease.
 - Acts by causing VD in internal ear.
- Betazole
 - H2 agonist.
 - Used in gastric function tests

HISTAMINE ANTAGONISTS- CLINICAL CLASSIFICATION:

- **H1 receptor antagonist**
- Sedative (first generation) antihistamines: Highly lipid soluble and easily enters into the CNS:
 - Potent and marked sedative:
 - Promethazine (phenergan) *widely used* • *Diphenhydramine Dimenhydrinate*
 - Potent and moderate sedative:
 - Chlorcyclizine • Chlorpheniramine • Tetrahydroxy carboline
 - Less potent and less sedative:
 - Mepyramine • Pheniramine(avigil) 25.
- Non-sedative (second generation) antihistamines: Less lipid soluble therefore cannot enter into the CNS:
 - Cetrizine • Terfenadine • Astemizole • Loratadine • Ketotifen • Cyclizine

H1 RECEPTOR ANTAGONISTS:

- Conventionally called antihistamines.
- Mechanism of action:
- H1 antihistamines antagonize the effects of histamine by competitively blocking the H1 receptors (competitive antagonism).

FIRST GENERATION H1 BLOCKERS:

- They are conventional antihistamines.

Pharmacological actions:

- Antagonism of histamine:
 - Bronchoconstriction.
 - Block Contraction of intestine, smooth muscle and triple response.
- Anti-allergic action:
 - Most of the manifestations of type 1 reactions are suppressed.
- CNS:
 - Produce variable degree of cns depression, sedation and drowsiness.
 - At toxic doses, excitement and convulsions are seen.
 - As most of these drugs are lipophilic, easily cross BBB and act on CNS .

- Anticholinergic action:
 - Dryness of mouth, blurring of vision, constipation, urinary retention.
- At higher doses act as local anesthetics. They block Na channels in excitable tissues.

PHARMACOKINETICS:

- Well absorbed orally and can be given parenteral.
- Widely distributed in body. Newer drugs penetrate brain poorly.
- Metabolized in liver and excreted in urine.
- Duration of action of most agents is 4-6 hrs generally.

SECOND GENERATION H1 BLOCKERS:

- Advantages over classical antihistamines:
 - Higher H1 selectivity: no anticholinergic side effects.
 - Do not impair psychomotor performance.
 - Absence of CNS depressant property. They poorly cross BBB.
 - Additional antiallergic mechanisms apart from histamine blockade: some also inhibit late phase allergic reaction by acting on leukotrienes or by antiplatelet activating factor effect.]
 - Some of them are long acting.

Table 6.1 Second-generation H₁-blockers

Drug	Route and duration of action	Important features
Cetirizine	PO, 12-24 h	<ul style="list-style-type: none">• H₁ blocker; inhibits histamine release; achieves good concentration in the skin; poorly crosses BBB; may cause drowsiness• Drug interactions rare
Levocetirizine	PO, 12-24 h	More potent and produces less adverse effects than cetirizine
Loratadine Desloratadine Mizolastine Ebastine	PO, 24 h	<ul style="list-style-type: none">• Long acting, non-sedating agents• Cardiac arrhythmias have been noticed in animals treated with ebastine• No cardiac arrhythmias with loratadine and desloratadine• Loratadine may rarely cause seizures
Fexofenadine	PO, 12-24 h	<ul style="list-style-type: none">• Active metabolite of terfenadine• Non-sedating agent• Arrhythmias rare; avoid in patients with prolonged QT interval
Azelastine	Topical (nasal spray, eye drops), 12-24 h	<ul style="list-style-type: none">• H₁ blocker; inhibits histamine release• Produces active metabolite• Has a rapid onset and long duration of action• Taste alteration, burning sensation in the nose, drowsiness
Rupatadine	PO	H ₁ blocker + blocks actions of platelet activating factor

THERAPEUTIC USES:

Allergic diseases:

- Oral antihistamines - of allergic rhinitis and urticaria because histamine is the principal mediator released by mast cells.
- Ophthalmic antihistamines, such as *azelastine* , *olopatadine* , *ketotifen* are useful for the treatment of allergic conjunctivitis.

Common cold:

- symptomatic relief by anticholinergic (reduce rhinorrhoea) and sedative actions.

Motion sickness:

- given 30 – 60 min before journey.
- Because of anticholinergic action.

Preanesthetic medication:

- Promethazine as sedative and anticholinergic.

- **Vertigo:**

- Cinnarizine inhibits vestibular sensory nuclei in the inner ear, suppresses postrotatory labyrinthine reflexes, possibly by reducing stimulated influx of Ca^{2+} from endolymph into the vestibular sensory cells.
- Beneficial effects have been reported in Ménière's disease and other types of vertigo.

- **Parkinsonism**

- Promethazine and diphenhydramine are used for the treatment of drug induced parkinsonism.

- ***Cough***

- *Antihistaminics like chlorpheniramine*, diphenhydramine and promethazine are used.
- no selective cough suppressant action, afford symptomatic relief by sedative and anticholinergic property .

- *As sedative, hypnotic, anxiolytic*
 - *Antihistamines* with CNS depressant action have been used as sedative and to induce sleep, especially in children.

ADVERSE EFFECTS:

- Common
 - Sedation, drowsiness, lack of concentration, headache, fatigue, weakness, lassitude, in coordination, etc.
- GIT side effects:
 - Nausea, vomiting, loss of appetite and epigastric discomfort.
- Anticholinergic:
 - Dry mouth, blurring of vision, constipation and urinary retention.
- Teratogenic
- Allergic reactions can occur

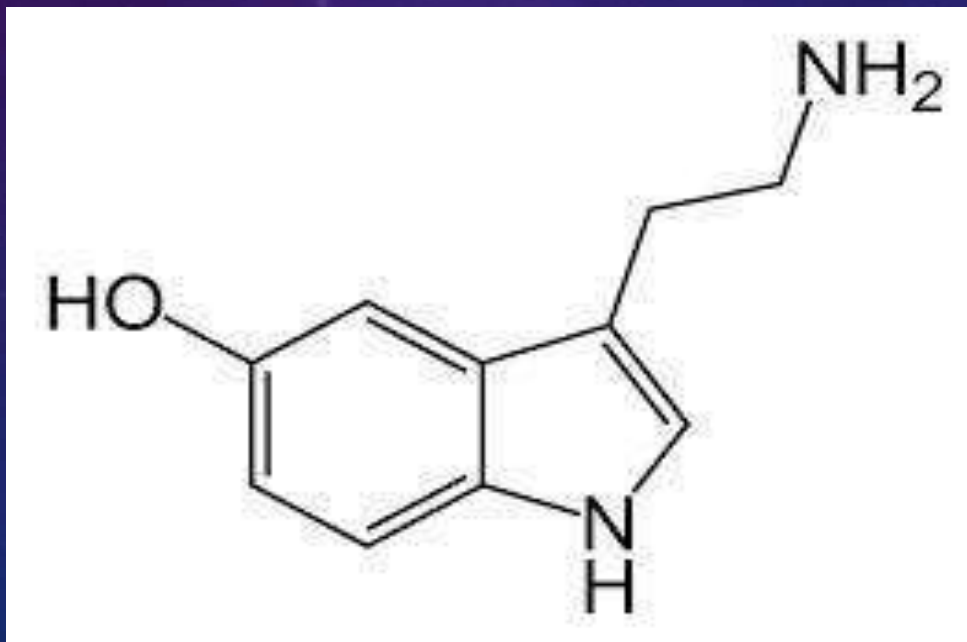
- H2 blockers:
 - Gastroselective antihistamines.
 - Cimetidine, ranitidine, nizatidine.
 - They reduce gastric secretion.
 - Treat peptic ulcer.
- H3 blockers:
 - They modulate the histaminergic neurotransmission in brain.
 - They have application in obesity, sleep disorders, neuropsychiatric disorders and cognitive functions.
 - Thioperamide and clobenpropit.
- H4 blockers:
 - Clobenpropit and thioperamide has partial action.

SEROTONIN

The background is a gradient from dark purple to blue, featuring a starry space pattern. On the right side, there are several technical diagrams, including a large circular scale with numerical markings (100, 120, 140, 160, 170, 180, 190, 200) and arrows, and other smaller circular diagrams with arrows, suggesting a scientific or technical theme.

INTRODUCTION:

- A monoamine neurotransmitter biochemically derived from tryptophan.
- Structurally it contains an indole ring, hydroxyl group and ethyl amine group attached to the ring.]



- Approximately 90% of the human body's total serotonin is located in the enterochromaffin cells in the alimentary canal (gut), used to regulate intestinal movements. Hence also called enteramine.

SYNTHESIS AND DEGRADATION:

- synthesized in serotonergic neurons of the CNS, where it has various functions including the regulation of mood, appetite, and sleep.
- Serotonin secreted from the enterochromaffin cells eventually finds its way out of tissues into the blood.
- There, it is actively taken up by blood platelets through their serotonin transporters, which store it. When the platelets bind to a clot, they release serotonin, where it serves as a vasoconstrictor and helps to regulate homeostasis and blood clotting.
- As it is a monoamine like CAs it is metabolized by MOA and also COMT.

TRYPTOPHAN



5-HYDROXYTRYPTOPHAN



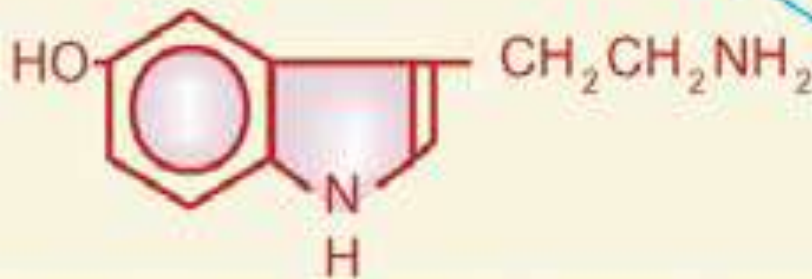
5-HT

MAO

5-HYDROXY INDOLE
ACETIC ACID
(5-HIAA)

Dehydrogenase

5-HYDROXY
TRYPTOPHOL



SEROTONIN RECEPTORS AND THEIR ACTIONS

- There are around 10 to 15 5 HT receptors. But there are 3 or 4 receptors on which drugs are synthesized.

receptor	Type and mechanism	location	actions	Agonist or antagonist
5-HT 1	Gi Dec in cAMP	<ul style="list-style-type: none"> •CNS (raphe nuclei and hippocampus) •cranial blood vessels 	<ul style="list-style-type: none"> •Dec 5HT release •Constriction of cranial BVs. •Decreased release of peptides from nerve endings. 	<ul style="list-style-type: none"> •Buspirone •Triptans (selective 5 HT 1b/1d) •Ergonometrin (partial antagonist)
5-HT2	Gq Increased IP3 and DAG	<ul style="list-style-type: none"> •Platelets •Smooth muscles •Cerebral cortex (2a) •Fundus of stomach(2B) •Choroid(2c) 	<ul style="list-style-type: none"> •Platelet aggregation. •Smooth muscle contra •(+) of neurons •CSF production. 	<ul style="list-style-type: none"> •2A antagonist- katanserin, cyproheptadine, atypical antipsychotics. •2A/2C antagonist- methysergide.
5-HT 3	Ligand gated Na and K channels	<ul style="list-style-type: none"> •CTZ •NTS •Parasymp nerve terminal (GIT) 	<ul style="list-style-type: none"> •Vomiting •Peristalsis •Stimulate neurons 	<ul style="list-style-type: none"> •Odansetron, granisetron (5-HT 3 antagonists)
5-HT 4	Gs Increased cAMP	<ul style="list-style-type: none"> •GIT •CNS 	<ul style="list-style-type: none"> •Peristalsis •Enhance gut secretions. 	<ul style="list-style-type: none"> •Agonists – renzapride, metoclopramide, prucalopride.

PHARMACOLOGICAL ACTIONS:

CVS:

- Triphasic response is seen on iv injection :
 - Early sharp fall in BP—due to coronary chemoreflex.
 - Brief rise in BP—due to vasoconstriction and increased cardiac output
 - Prolonged fall in BP—due to arteriolar dilatation and extravasation of fluid.
- But has no role in physiological regulation of bp.

On GIT smooth muscles:

- Increased contractions and secretions.

On nerve endings and adrenal medulla:

- Stimulation and release of CAs.

On respiratory tract:

- Stimulation of resp and hyperventilation

Platelets:

- Changes in shape of platelets and aggregation.

CNS:

- Injected i.v., 5-HT does not produce central effects, poorly crosses BBB.
- serves as a transmitter primarily inhibitory.
- Direct injection in the brain produces sleepiness, changes in body temperature, hunger and a variety of behavioral effects

PATHOPHYSIOLOGICAL ROLES:

- ***Neurotransmitter:***
 - *5-HT is a confirmed neurotransmitter* in the brain 5-HT is probably involved in sleep, temperature regulation, thought, cognitive function, behaviour and mood (imbalance may result in affective disorders and schizophrenia), vomiting and pain perception.
- ***Precursor of melatonin in pineal gland.***
 - regulate biological clock and maintain circadian rhythm.
- ***Neuroendocrine function:***
 - control release of anterior pituitary hormones.
- ***Nausea and vomiting are evoked.***
- ***Migraine***
 - *5-HT is said to initiate the vasoconstrictor* phase of migraine and to participate in neurogenic inflammation of the affected blood vessels.

- **Maintain homeostasis:**
 - accelerates platelet aggregation and clot formation.
 - Its contractile action appears to promote retraction of the injured vessel.
- Both the above actions contribute to haemostasis.
- ***Raynaud's phenomenon:***
 - *Release of 5-HT* from platelets may trigger acute vasospastic episodes of larger arteries.
- ***Variant angina:***
 - *Along with thromboxane A₂*, 5-HT released from platelets has been implicated in causing coronary spasm and variant angina.
- ***Intestinal motility:***
 - *Enterochromaffin cells and 5-HT* containing neurones may regulate peristalsis and local reflexes in the gut.

SEROTONIN AGONISTS

Triptans:

- Sumatriptin:
 - 5HT 1D/1B agonist – block the release of vasodilator peptides by acting on presynaptic trigeminal nerve ending.
 - Constrict the cerebral blood vessels and prevent stretching of pain nerve endings.
 - Given orally/SC.
 - Bioavailability 14 percent and short acting half-life 2 hr.
- Uses:
 - Treat migraine and cluster headache.
 - Suppress nausea and vomiting of migraine.
- ADR:
 - Dizziness, altered sensations, weakness, chest discomfort and neck pain.
- Zolmitriptan, almotriptan, frovatriptan, rizatriptan, naratriptan are others.

Other agonists:

- Buspirone 5-HT 1a agonist-antagonist. Used as antianxiety agent.
- Cisapride 5HT 4 agonist. Prokinetic agent.
- Tegaserod 5 HT 4 agonist. Used in irritable bowel syndrome.
- Dexfenfluramine- appetite suppressant.
- SSRIs – fluoxetine .

SEROTONIN ANTAGONISTS:

Drug	Act as	uses	Side effects
Cyproheptadine:	H1, 5-HT 2a blocker.	Sedative and anticholinergic. Increases appetite, Carcinoid and post gastrectomy dumping syndrome.	Drymouth, dorwsiness wait gain.
ketanserin	5-HT 2A and alpha (-)	Antihypertensive	
Odansetron and granlsetron	5 HT 3 blocker	antiemeric	
Atypical antipsychotics Clozapine, olanzepine,	5 HT 2 BLOCKER	Schizophrenia	
methysergide	5 HT 2A/2C blocker	Prophylaxis of migrane	Chronic use causes abdominal and pulmonary fibrosis.
ergotamine	5 HT 1 partial agonist/ antagonist	Acute attack of migrane	Nausea, vomiting , diarrhoea are common
Ergometrin	5 HT 1 partial agonist/ antagonist	Postpartum haemorrhage	Chronic- persistant vasospasam

PROSTAGLANDIDS AND THROMBOXANES

The background features a blue gradient with faint technical diagrams. On the right side, there are circular gauges with numerical scales (e.g., 100, 120, 140, 160, 180, 200) and arrows. There are also dashed lines and other circular patterns scattered across the background.

INTRODUCTION:

- Group of hormone-like lipid compounds
- Derived enzymatically from fatty acids
- Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring.
- They are produced in many places throughout the body and their target cells are present in the immediate vicinity of the site of their secretion.
- The prostaglandins, together with the thromboxane and prostacyclin, form the prostanoid class of fatty acid derivatives, a subclass of eicosanoids.
- They are autocrine and paracrine lipid mediators that act upon platelets, endothelium, uterine and mast cells. They are synthesized in the cell from the essential fatty acids (EFAs).

- Arachidonic acid is the precursor for the biosynthesis of all PGs. And the enzyme involved is COX (cyclooxygenase).

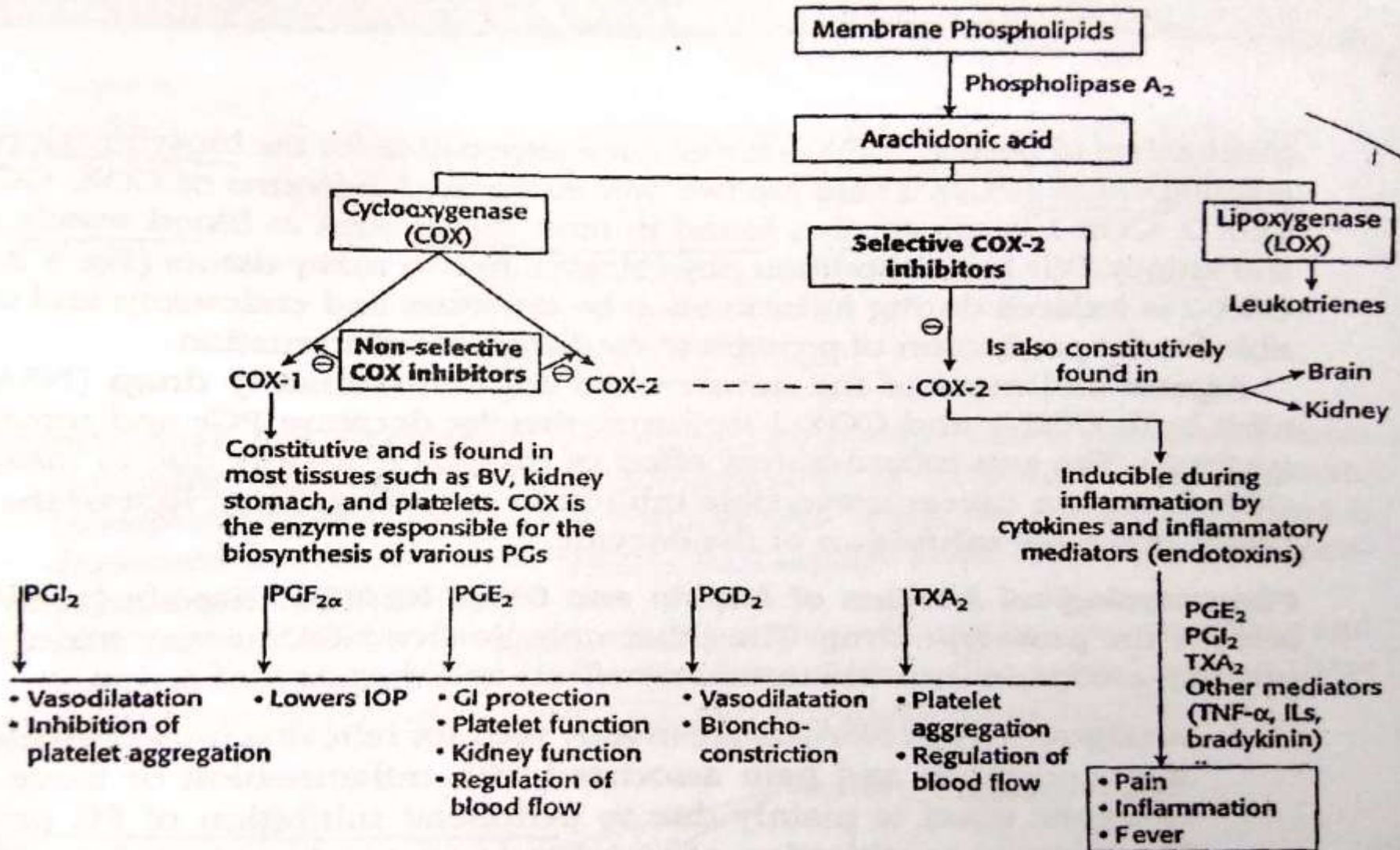
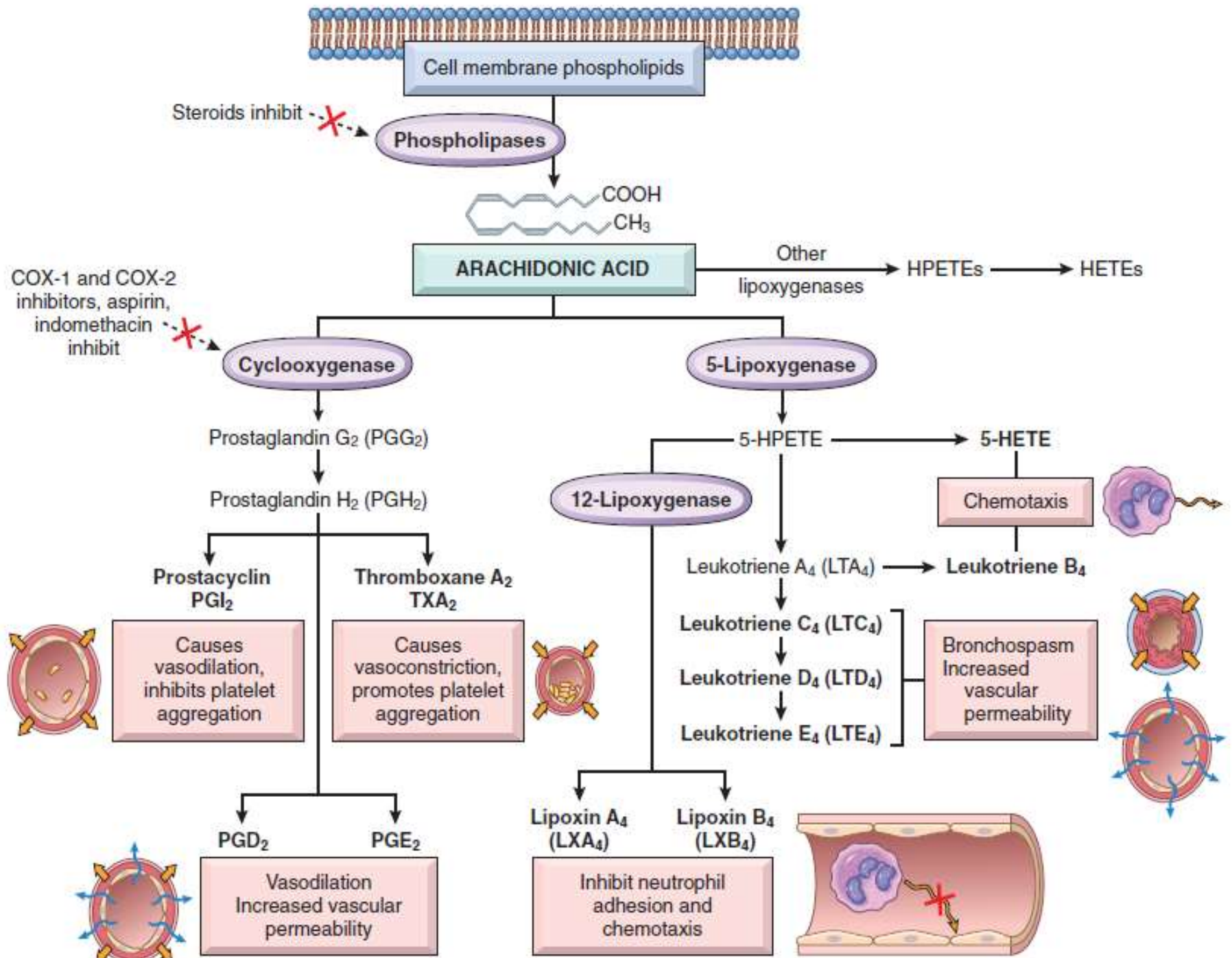


FIGURE 6.2 The different roles of cyclooxygenases (COX-1 and COX-2) and the drugs inhibiting them. BV, Blood vessels.



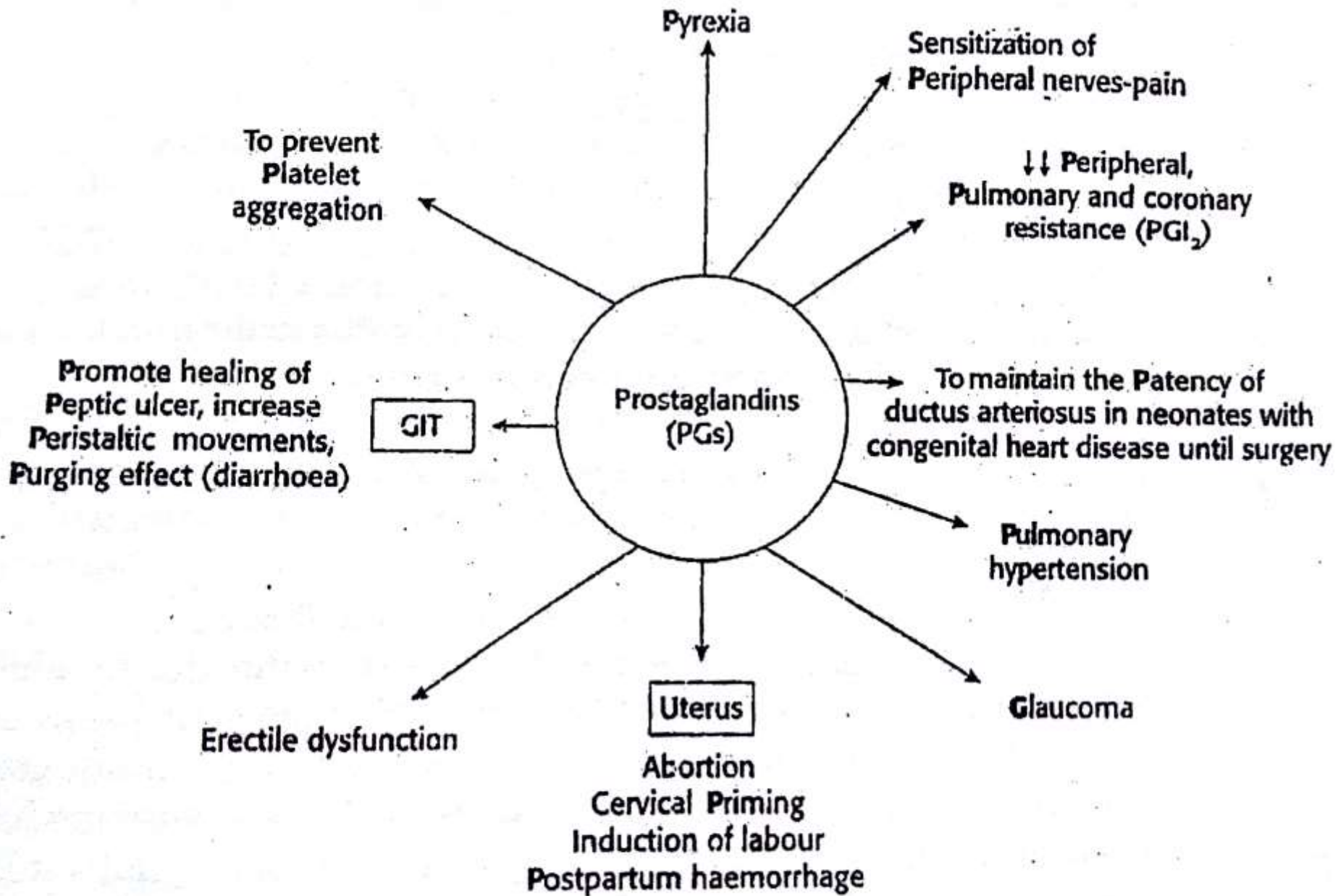


FIGURE 6.3 Effects and uses of prostaglandins.

PROSTANOID RECEPTORS:

- PGs act on prostanoid receptors to show their action.
- All are GPCRs.
- There are five classes of prostanoid receptors. They are –
 - DP (for PGD₂) – subtypes DP1 and DP2
 - EP (for PGE₂) – subtypes EP1 and EP4
 - FP (for PGF₂ alpha)
 - IP (for PGI₂)
 - TP (for TXA₂)

Full name	shortened name	activating prostanoids	classification ^[5]	G protein linkage ^[2]	pathways ^[2]
Prostaglandin DP1 receptor	DP ₁	PGD ₂ >>PGE ₂ >PGF ₂ α>PGI ₂ =TXA ₂ ^[6]	relaxant	Gs alpha subunit	activates AC, increases cAMP, raises Ca ²⁺
Prostaglandin DP2 receptor	DP ₂	PGD ₂ >>PGF ₂ α=PGE ₂ >PGI ₂ =TXA ₂ ^[7]	?	Gi alpha subunit	inhibits AC to depress cAMP levels
Prostaglandin EP1 receptor	EP ₁	PGE ₂ >PGF ₂ α=PGI ₂ >PGD ₂ =TXA ₂ ^[8]	contractile	Gq alpha subunit	stimulates PLC, IP ₃ , PKC, ERK, p38 Mpk, and CREB
Prostaglandin EP2 receptor	EP ₂	PGE ₂ >PGF ₂ α=PGI ₂ >PGD ₂ =TXA ₂ ^[9]	relaxant	Gs alpha subunit	stimulates AC, raises cAMP, stimulates beta catenin and Glycogen synthase kinase 3
Prostaglandin EP3 receptor	EP ₃	PGE ₂ >PGF ₂ α,PGI ₂ >PGD ₂ =TXA ₂ ^[10]	inhibitory	Gi & G12 subunit	inhibits AC, decreases cAMP, stimulates PLC & IP ₃ , raises Ca ²⁺
Prostaglandin EP4 receptor	EP ₄	PGE ₂ >PGF ₂ α=PGI ₂ >PGD ₂ =TXA ₂ ^[11]	relaxant	Gs alpha subunit	stimulates AC, PKA, PI3K, AKT, ERK, p38 Mpk, & CREB; raises cAMP
Prostaglandin F2α receptor	FP	PGF ₂ α>PGD ₂ >PGE ₂ >PGI ₂ =TXA ₂ ^[12]	contractile	Gq alpha subunit	stimulates PLC, IP ₃ , & PKC; raises Ca ²⁺
Prostacyclin I2 receptor	IP	PGI ₂ >>PGD ₂ =PGE ₂ =PGF ₂ α>TXA ₂ ^[13]	relaxant	Gs alpha subunit	stimulates AC & PKA; raises cAMP
Thromboxane A2 receptor	TP	TXA=PGH ₂ >>PGD ₂ =PGE ₂ =PGF ₂ α=PGI ₂ ^[14]	contractile	Gq alpha subunit	stimulates PLC & IP ₃ ; raises Ca ²⁺

PHARMACOLOGICAL ACTIONS:

- On CVS:

mediator	action	role
PGD2	VD	
PGE2	VD	Maintain patency of ductus arteriosus before surgery.
PGI 2	VD	Dec peripheral, pulmonary and coronary resistance Regulate local vascular tone.
PGF2 α	VC pulmonary V&A VD	Stimulate heart by prominent reflex action due to fall in BP. The CO increases.
TXA 2	VC	

- On GIT:
 - PGI₂ and PGE₂ – dec acid secretion and inc mucus secretion. And also increase peristalsis.
 - PGE₁ – reduce NSAIDS induced ulcers.
- Airways:
 - PGF₂ α , PGD₂ and TXA₂ – are potent bronchoconstrictors.
 - PGE₂ is a powerful bronchodilator.
 - PGI₂ produces mild dilatation.
- Platelets:
 - TXA₂, produced locally by platelets, is a potent inducer of aggregation.
 - PGG₂ and PGH₂ are also proaggregatory.
 - PGI₂- potent inhibitor of platelet aggregation.
 - PGD₂ has antiaggregatory action. Less potent

- Eyes:
 - $\text{PGF}_2\alpha$ induces ocular inflammation and lowers i.o.t by enhancing uveoscleral outflow.
 - Used in glaucoma.
- Kidneys:
 - PGE_2 and PGI_2 increase water, Na^+ and K^+ excretion and have a diuretic effect.
 - PGE_2 has furosemide-like inhibitory effect on Cl^- reabsorption as well.
 - They cause renal vasodilatation and inhibit tubular reabsorption. PGE_2 antagonizes ADH action, and this adds to the diuretic effect.
 - TXA_2 causes renal vasoconstriction.
 - PGI_2 , PGE_2 and PGD_2 evoke release of renin.
- CNS:
 - injected intracerebroventricularly
 - PGE_2 produces a variety—sedation, rigidity, behavioral changes and marked rise in body temperature.
 - PGI_2 also induces fever, but TXA_2 is not pyrogenic.
- PNS:
 - both inhibition as well as augmentation of NA release from adrenergic nerve endings has been observed.
 - PGs may modulate sympathetic neurotransmission in the periphery.

- Reproductive system:
 - Female reproductive system:
 - Uterus:
 - PGE 2 & PGF2 α –
 - contract pregnant uterus.
 - Induce labor at term
 - Cervical priming.
 - Control PPH.
 - Male reproductive system:
 - PGs facilitate motility of sperms and fertilization by coordinating the movement of the uterus.
- **Endocrine system :**
 - **PGE2 facilitates** release of anterior pituitary hormones—growth hormone, prolactin, ACTH, FSH and LH as well as that of insulin and adrenal steroids.
 - It has a TSH like effect on thyroid.

<i>Organ</i>	<i>Prostaglandin E₁ (PGE₁)</i>	<i>Prostaglandin F_{2α} (PGF_{2α})</i>	<i>Prostacyclin (PGI₁)</i>	<i>Thromboxane A₁ (TXA₁)</i>
1. Blood vessels	Vasodilatation, ↓ BP	Vasodilatation (mostly), larger veins constrict, little effect on BP	Vasodilatation (marked and widespread), ↓ ↓ BP	Vasoconstriction
2. Heart	Weak inotropic, reflex cardiac stimulation	Weak inotropic	—	—
3. Platelets	Variable effect	—	Antiaggregatory	Aggregation and release reaction
4. Uterus	Contraction (<i>in vivo</i>), relaxes nongravid human uterus <i>in vitro</i> , softening of cervix	Contraction (<i>in vivo</i> and <i>in vitro</i>), softening of cervix	—	—
5. Bronchi	Dilatation, Inhibit histamine release	Constriction	Dilatation (mild), inhibit histamine release	Constriction
6. Stomach	↓ acid secretion, ↑ mucus production	—	↓ acid secretion (weak), mucosal vasodilatation	—
7. Intestine	Contracts longitudinal & relaxes circular muscles, ↑ peristalsis, ↑ Cl ⁻ & water secretion	Spasmogenic, ↑ fluid & electrolyte secretion (weak)	Weak spasmogenic, inhibit toxin-induced fluid secretion	Weak spasmogenic
8. Kidney	Natriuresis, ↓ Cl ⁻ reabsorption, inhibit ADH action, vasodilatation, renin release	—	Natriuresis, vasodilatation, renin release	Vasoconstriction
9. CNS	Pyrogenic, variety of effects on i.c.v. inj.			
10. Release of NA	↑ or ↓	↑ or ↓		
11. Afferent nerves	Sensitize to noxious stimuli → tenderness	—	Same as PGE ₂	—
12. Endocrine system	Release of ant. pituitary hormones, steroids, insulin; TSH-like action	Release of gonadotropins & prolactin, luteolysis (in animals)	—	—
13. Metabolism	Antilipolytic, insulin like action, mobilization of bone Ca ²⁺	—	—	—

THERAPEUTIC USES:

- Gynecological and obstetrical:
 - Abortion:
 - PGE 2 and PGF 2 alpha stimulate uterine contractions and cause ripening of cervix.
 - Facilitation of labor:
 - PGE 2 used
 - Soften cervix for induction of labor.
 - PPH:
 - PGF 2 alpha used alternative to ergometrine.
- GIT:
 - PGE 1 & 2 – prevent peptic ulcer on high dose of NSAIDs.
- CVS:Patent ductus arteriosus
- Glaucoma
 - PGF 2 alpha reduce i.o.t
- Peripheraal vacular diseases
- Pulmonary hypertension
- Erectile dysfunction

Table 35.1 Preparations and uses of prostaglandin analogs

<i>PG Analog</i>	<i>PG Type</i>	<i>Preparation and routes of administration</i>	<i>Indications</i>
Misoprostol	PGE ₁	MISO 200 mcg tab 2 tabs oral	Abortion (along with mifepristone)
Gemeprost	PGE ₁	CERVAGEM 1mg vaginal pessary	Cervical priming, Midtrimester abortion.
Alprostil	PGE ₂	2.5–25 mcg intra cavernosal inj /intraurethral pessary	Erectile dysfunction, to maintain patency of ductus arteriosus
Dinoprostone	PGF _{2α}	0.5 mg vaginal gel, cervical gel, vaginal tab Extra-amniotic solution, IV inj PROSTIN- E, PRIMIPROST, CERVIPRIME	Induction/facilitation of labour, midterm abortion.
Dinoprost	PGF _{2α}	PROSTIN F _{2α} 5 mg/ml intraamniotic inj	Midterm abortion, Induction of labour
Latanoprost, Bimatoprost	PGF _{2α}	LATOPROST 0.0005% eye drops - 1 drop every evening	Glaucoma
Epoprostanol	PGI ₂	IV FLOLAN 0.5 mg inj	To prevent platelet aggregation in cardiopulmonary bypass, pulmonary hypertension

Rioplast - PGE₁ analog and enprostil - PGE₂ analog - preparations are not available in India at present.

ADVERSE EFFECTS

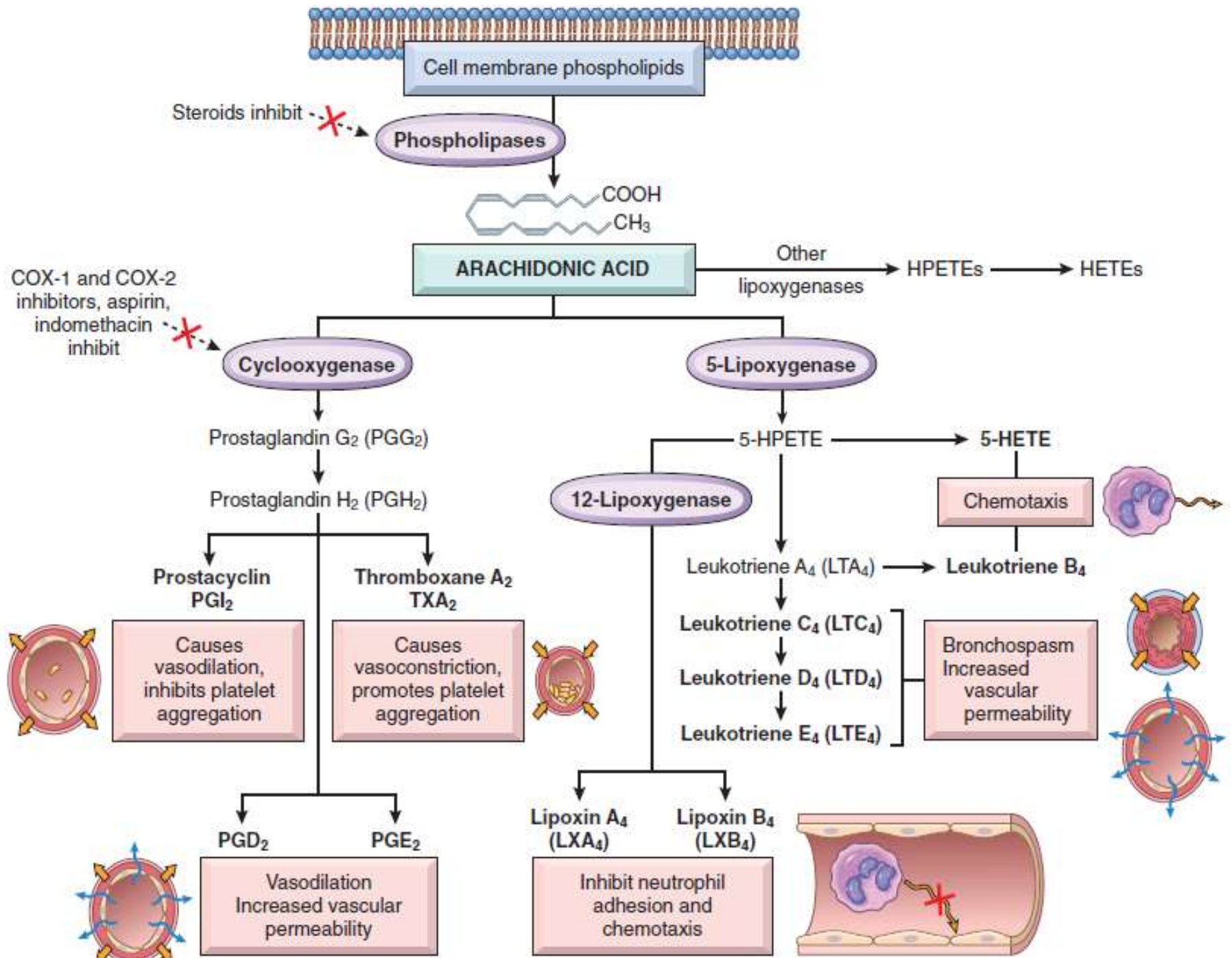
- Depending upon dose, type of PG and route.
- Diarrhoea, nausea, vomiting, fever, hypotension and pain are common
- unduly forceful uterine contractions, vaginal bleeding, flushing, shivering, fever, malaise, fall in BP, tachycardia, chest pain.

LEUKOTRIENES

The background is a gradient from dark purple to blue, featuring faint technical diagrams and a starry space pattern. On the right side, there are several circular diagrams with concentric lines and arrows, resembling a gauge or a control panel. One of these diagrams has numerical markings from 80 to 200. There are also some dashed lines and arrows pointing in various directions, suggesting a complex system or process.

INTRODUCTION:

- Leukotrienes are so named because they were first obtained from leukocytes (leuko) and conjugated double bonds
- The straight chain lipoxygenase products of arachidonic acid are produced by a more limited number of tissues (LTB₄ mainly by neutrophils; LTC₄ and LTD₄—the cysteinyl LTs—mainly by macrophages), but probably they are pathophysiologically as important as PGs.



ACTIONS:

- On CVS and blood.
 - LTC₄ and LTD₄ injected i.v. evoke a brief rise in BP followed by a more prolonged fall. It is probably a result of coronary constriction induced decrease in cardiac output and reduction in circulating volume due to increased capillary permeability.
 - markedly increase capillary permeability .
 - LTB₄ is highly chemotactic for neutrophils and monocytes.
 - LTC₄ and D₄ cause exudation of plasma
- Smooth muscles:
 - LTC₄ and D₄ contract most smooth muscles.
 - They are potent bronchoconstrictors and induce spastic contraction of g.i.t. at low concentrations.
 - They also increase mucus secretion in the airways
- **Afferent nerves**
 - Like PGE₂ and I₂, the LTB₄ also sensitizes afferents carrying pain impulses—
 - contributes to pain and tenderness of inflammation.

LEUKOTRIENE RECEPTORS:

- Separate receptors for LTB₄ (BLT) and for the cysteinyl LTs (LTC₄, LTD₄) have been defined.
- Two subtypes,
- *Cys LT1 and cysLT2 of the cysteinyl LT receptor have been cloned.*
- All LT receptors function through the IP₃/DAG transducer mechanism.

LEUKOTRIENES IN ASTHMA

- Leukotrienes assist in the pathophysiology of asthma, causing or potentiating the following symptoms:
 - airflow obstruction
 - increased secretion of mucus
 - mucosal accumulation
 - bronchoconstriction
 - infiltration of inflammatory cells in the airway wall

LEUKOTRIENE RECEPTOR ANTAGONIST

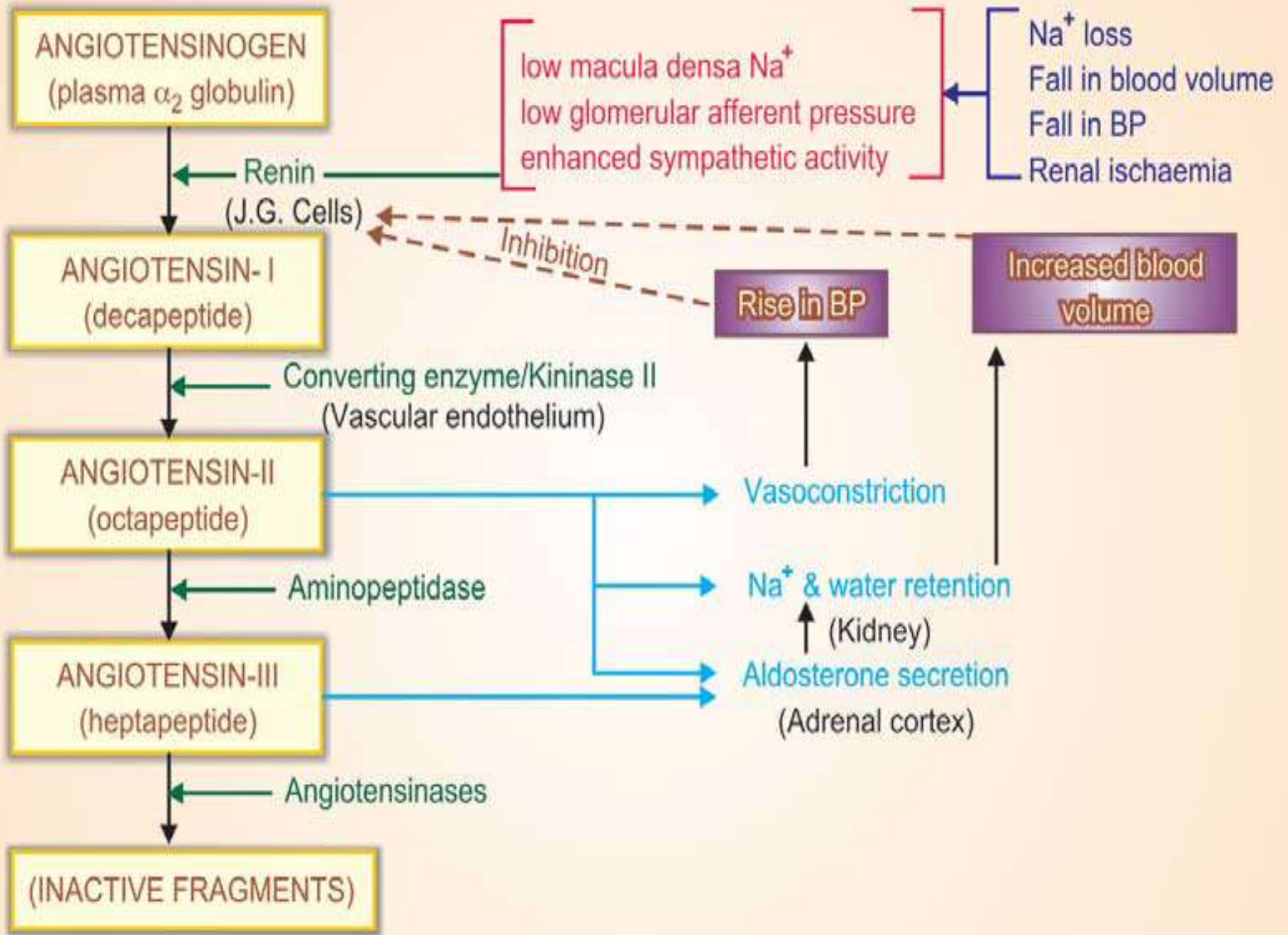
- **Mechanism of Action:**
- Attenuates bronchoconstriction and inflammation
 - Leukotriene Receptor Antagonists
 - Zafirlukast (Accolate)
 - Montelukast (Singulair)
 - Leukotriene Synthesis Inhibitor
 - Zileuton (Zyflo)

USED IN PROPHYLAXIS

- Chronic asthma
- Allergic Rhinitis
- Chronic Urticaria
- COPD
- Atopic Dermatitis
- Migraine Prophylaxis
- Sino nasal polyposis

ANGIOTENSIN:

- *Angiotensin-II (A-II) is an octapeptide generated in the plasma from a precursor plasma α_2 globulin, and is involved in electrolyte, blood volume and pressure homeostasis.*
- RAAS



ANGIOTENSIN RECEPTORS:

- Specific angiotensin receptors are present on the surface of target cells.
- Two subtypes (AT1 and AT2) have been differentiated pharmacologically.
- Both are GPCRs.
- **AT1:**
- Location:
 - Found in the heart, blood vessels, kidney, adrenal cortex, lung and brain and mediates the vasoconstrictor effects.
- mechanism:
 - The activated receptor in turn couples to $G_{q/11}$ and $G_{i/o}$ and thus activates phospholipase C and increases the cytosolic Ca^{2+} concentrations, which in turn triggers cellular responses such as stimulation of protein kinase C.
- Effects:
 - vasoconstriction, aldosterone synthesis and secretion, vasopressin secretion, cardiac hypertrophy, augmentation of peripheral noradrenergic activity, vascular smooth muscle cells proliferation, decreased renal blood flow, renal renin inhibition, renal tubular sodium reuptake, modulation of central sympathetic nervous system activity, cardiac contractility, central osmo control and extracellular matrix formation.

- AT 2:
- More plentiful in the fetus and brain, kidney, vascular endothelium.
- Effects:
 - Inhibition of cell growth, fetal tissue development, modulation of extracellular matrix, neuronal regeneration, apoptosis, cellular differentiation, and maybe vasodilation and left ventricular hypertroph

ACTIONS:

- CVS:
 - vasoconstriction—produced directly as well as
 - Increasing central sympathetic outflow.
 - Vasoconstriction involves arterioles and venules and occurs in all vascular beds.
 - BP rises acutely
 - Increases force of myocardial contraction by promoting Ca^{2+} influx.
 - Promotes the growth of vascular and cardiac muscle cells and may play a role in the development of cardiac hypertrophy.
- Adrenal cortex:
 - enhance synthesis and release of aldosterone which acts on distal tubule to promote Na^+ reabsorption and K^+/H^+ excretion.

- **Kidney:**
 - A-II promotes Na^+/H^+ exchange in proximal tubule → increased Na^+ , Cl^- and HCO_3^- reabsorption.
 - Further, it reduces renal blood flow and produces intrarenal haemodynamic effects which normally result in Na^+ and water retention
- **CNS**
 - Angiotensin-II can gain access to certain periventricular areas of the brain to induce drinking behaviour and ADH release.
- **PERIPHERAL SYMPATHETIC STRUCTURES**
 - Releases adrenaline from adrenal medulla, stimulates autonomic ganglia, and increases output of NA from adrenergic nerve endings.

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM INHIBITORS

- SYMPATHETIC BLOCKERS (beta blockers):
 - Propranolol, Metoprolol, Esmolol
- RENIN INHIBITORY PEPTIDES:
 - Aliskerin
- ANGIOTENSIN CONVERTING ENZYME INHIBITOR:
 - Captopril, Enalapril, Ramipril
- ANGIOTENSIN RECEPTOR ANTAGONIST:
 - Candesartan, Valsartan, Telmisartan, Olmesartan
- ALDOSTERONE ANTAGONIST:
 - Spironolactone, Prorenone

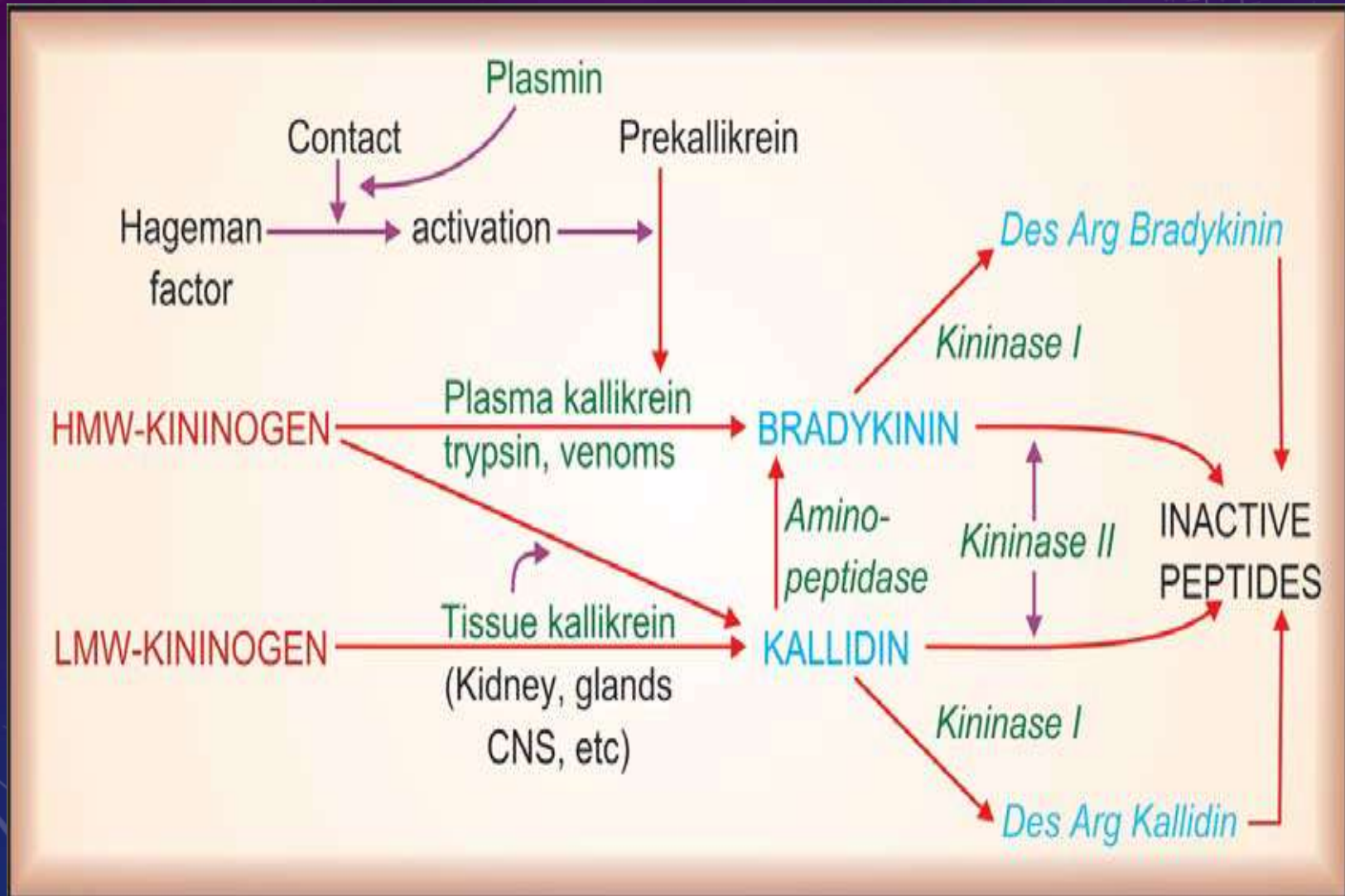
BRADYKININ:

The background is a dark blue gradient with a subtle pattern of white stars. Overlaid on this are several faint, light blue technical diagrams. On the right side, there is a large circular diagram with concentric circles and radial lines, resembling a scale or a gauge, with numbers ranging from 80 to 200. Below it is another circular diagram with dashed lines and arrows. In the bottom left corner, there is a partial circular diagram with a dashed arrow pointing left.

INTRODUCTION:

- It is a plasma kinin.
- Plasma kinins are polypeptides split off from a plasma globulin *Kininogen* by *the action of specific enzymes Kallikreins*
- Bradykinin is plasma kinin produced by the liver and present in plasma.
- It is nonapeptide.

GENERATION AND DEGRADATION OF PLASMA KININS:



ACTIONS:

- **CVS:**
 - more potent vasodilators than ACh and histamine.
 - The dilatation is mediated through endothelial NO and PGI₂ generation, and involves mainly the arterioles.
 - Larger arteries, most veins and vessels with damaged endothelium are constricted through direct action on the smooth muscle.
 - In addition, they can release histamine and other mediators from mast cells.
 - Kinins have no direct action on heart; reflex stimulation occurs due to fall in BP.
- **Smooth muscle:**
 - Kinin induced contraction of intestine is slow (*bradys—slow, kinein—to move*).
 - marked bronchoconstriction in asthmatic patients.

- **Neurones:**

- stimulate nerve endings that transmit pain and produce a burning sensation.
- Kinins release CAs from adrenal medulla.
- Injected directly in brain they produce a variety of effects including enhanced sympathetic discharge.
- They increase permeability of the blood brain barrier.

- **Kidney:**

- Kinins increase renal blood flow as well as facilitate salt and water excretion by action on tubules.
- The diuretic effect of furosemide is reduced by kinin B2 receptor antagonists, indicating participation of locally generated kinins in this response.

KININ RECEPTORS:

- two types of kinin receptors
- Bradykinin has higher affinity for B2 than for B1 receptors
- B1
 - located on the smooth muscle of large arteries and veins—mediates contraction of these vessels.
 - Inflammation induces synthesis of B1 receptors, so that they might play a major role at inflamed sites.
- B2
 - present on:
 - Visceral smooth muscle—contraction of intestine, uterus, airway.
 - Vascular endothelium—NO release, vasodilatation, increased permeability.
 - Sensory nerves—acute pain.

PATHOPHYSIOLOGICAL ROLES:

- *Mediation of inflammation*
 - *Kinins produce all the signs of inflammation—redness, exudation, pain and leukocyte mobilization.*
- *Mediation of pain*
 - *By directly stimulating nerve endings and by increasing PG production kinins appear to serve as mediators of pain.*
- Production of kinins is integrated with *clotting, fibrinolysin and complement systems.*

- Kinins cause closure of ductus arteriosus, dilatation of foetal pulmonary artery and constriction of umbilical vessels.
- Role in angioedema.
- also appear to be involved in *shock, rhinitis, asthma, ACE inhibitor induced cough, carcinoid, postgastrectomy dumping syndrome, fluid secretion in diarrhoea, acute pancreatitis and certain immunological reactions.*

BRADYKININ ANTAGONISTS:

- ***Deltibant*** :
 - It is a novel Bradykinin Antagonist used in treatment of Severe Systemic Inflammatory Response Syndrome and Sepsis.
- ***Icatibant*** :
 - It is a synthetic decapeptide functioning as a potent, competitive antagonist of the bradykinin 2 receptor
 - used in management of Hereditary angioedema