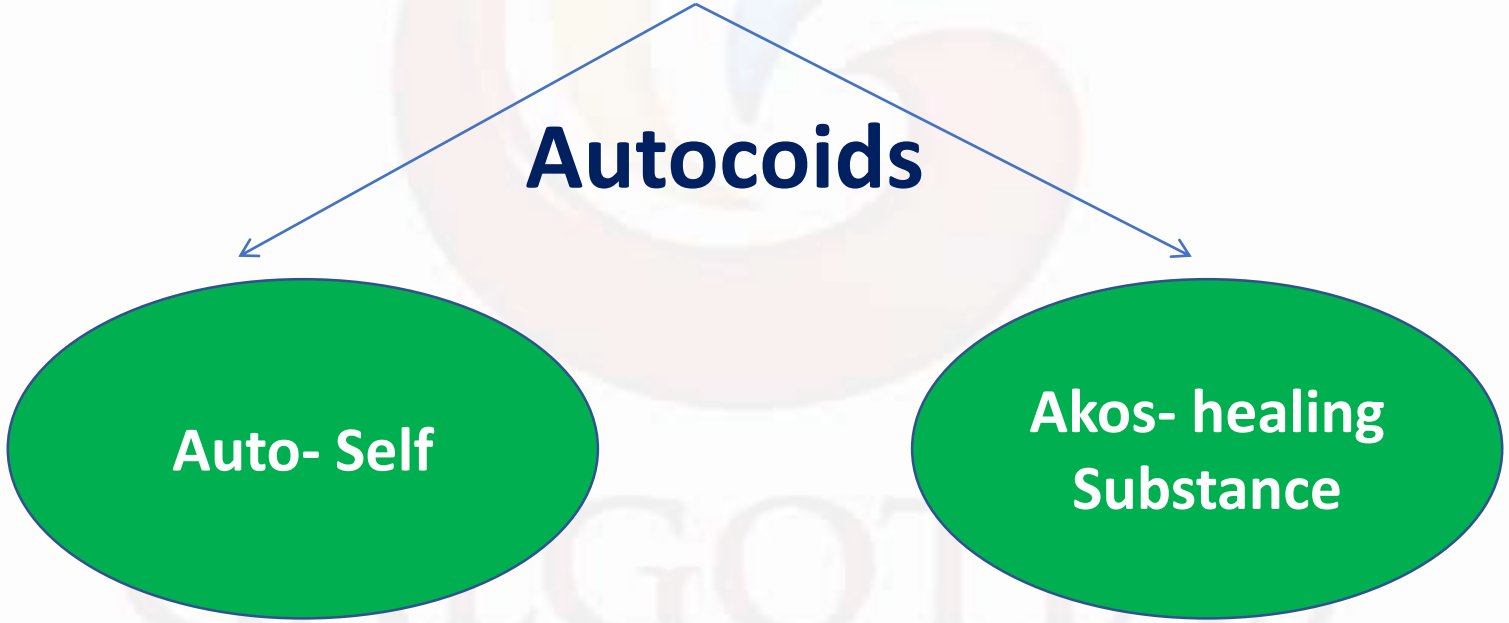
Autocoids and Related drugs

Disclaimer

All the content material provided here is only for teaching purpose.

Autocoids

These are the biochemical produced by a variety of cells in the body and capable of producing many biological functions. As they all produced actions at the site of synthesis and release so they are also called as Local hormone.



Types of Autocoids

On the basis of Chemical nature, Autocoids are classified in to three categories

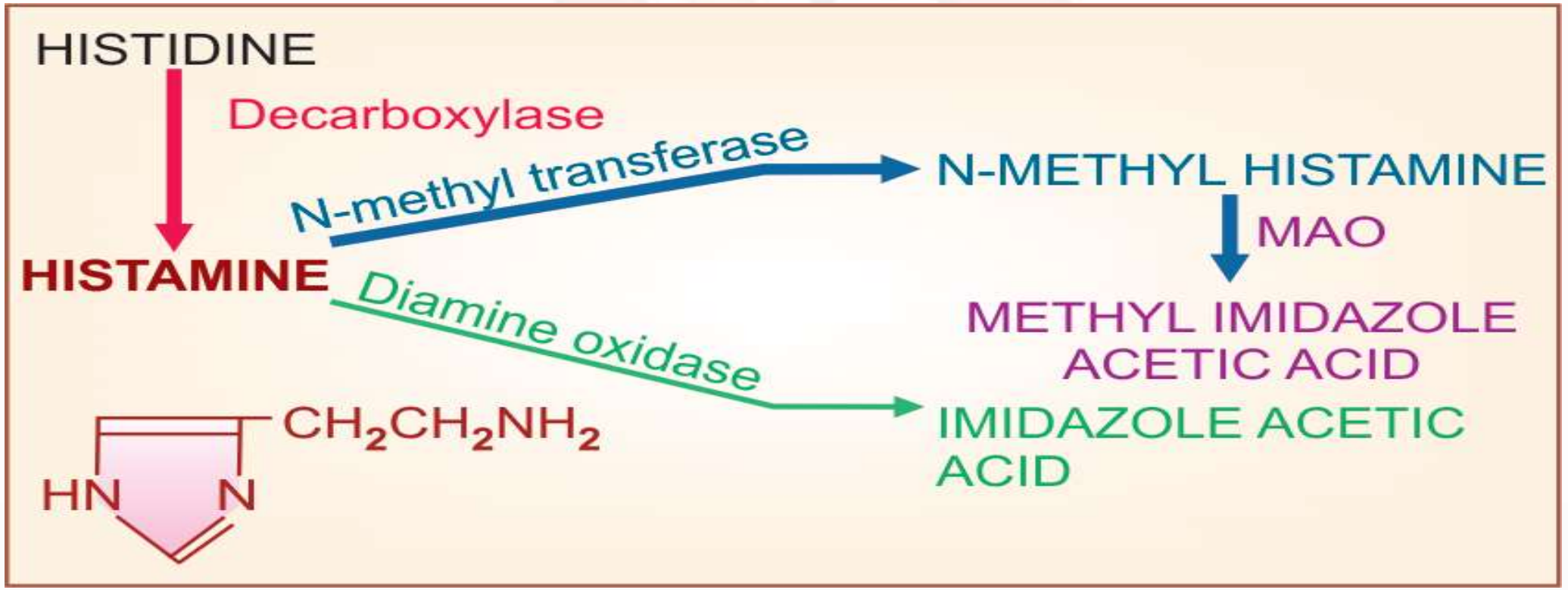
1. **Amine derivative:**
   - Histamine
   - Serotonin
2. **Peptide derivative:**
   - Angiotensin
   - Bradykinin
3. **Lipid derivative:**
   - Prostaglandins
   - Leukotrienes
   - Interleukins
   - Platelet Activating Factor,

Histamine

- Histamine means tissue amine.
- It is formed from the amino acid Histidine.
- It is very important mediator of inflammation.
- It also plays important role in anaphylaxis, allergies, gastric acid secretion and drug reaction.
- It is produced by mast cells and basophile cells during immune response against foreign pathogen.

Synthesis and metabolism of histamine

Histamine is β imidazolylethylamine. It is synthesized locally from the amino acid histidine and degraded rapidly by oxidation and methylation



Histamine receptors

receptor	mechanism	Location and function	agonists	Antagonsits
H1	Gq type IP3/DAG : Release of Ca2+ Pk-C activation	Smooth muscle (GIT, airway, uterus)- contraction blood vessels: Endothelium- VD Smooth muscle - VC brain – transmitter Adrenal – release of CAs.	methyl histamine, 2-pyridyl ethylamine	Mepyramine, Chlorphenaramine,
H2	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
H3	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	Thioperaminde, impromidine, ciproflaxacin
H4	G I Dec in c AMP	Mediate mast cell chemotaxis		Thioperamide

Actions of Histamine:

- 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 headche.

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:

Chloryclizine • Chlorpheniramine • Tetrahydeoxy carboline

Less potent and less sedative:

Mepyramine • Pheniramine(avil) 25.

- Non-sedative (second generation) antihistamines: Less lipid soluble therefore cannot enter into the CNS:

  Cetrizine • Terfenadine • Astemizole • Loratadine • Ketotifen • Cyclizine

Histamine Antagonists:

H1 ANTAGONISTS:

1. **Antagonism of histamine- B**lock histamine induced bronchoconstriction
2. **Antiallergic action- Suppression of hypersenstivity reaction**
3. **CNS- Depression**
4. **Anticholinergic action- Antagonism of muscarinic action.**
5. **BP- Fall in B.P.**

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 ANTIHISTAMINICS

- **Fexofenadine**
- **Loratadine**
- **Desloratadine**
- **Cetirizine**
- **Levocetirizine**

Uses:

- *Allergic disorders*
- *Pruritides*
- *Common cold*
- *Motion sickness*
- *Vertigo*
- *Preanaesthetic medication*
- *Cough*
- *As sedative, hypnotic, anxiolytic*

ADVERSE EFFECTS:

- Common

Sedation, drowsiness, lack of concentration, headache, fatigue, weakness, lasstitude, in coordination, etc.

- GIT side effects:

Nausea, vomiting, loss of appetite and epigastric discomfort.

- Anticholinergic:

Dry mouth, blurring of vision, constipation and urinary retention.

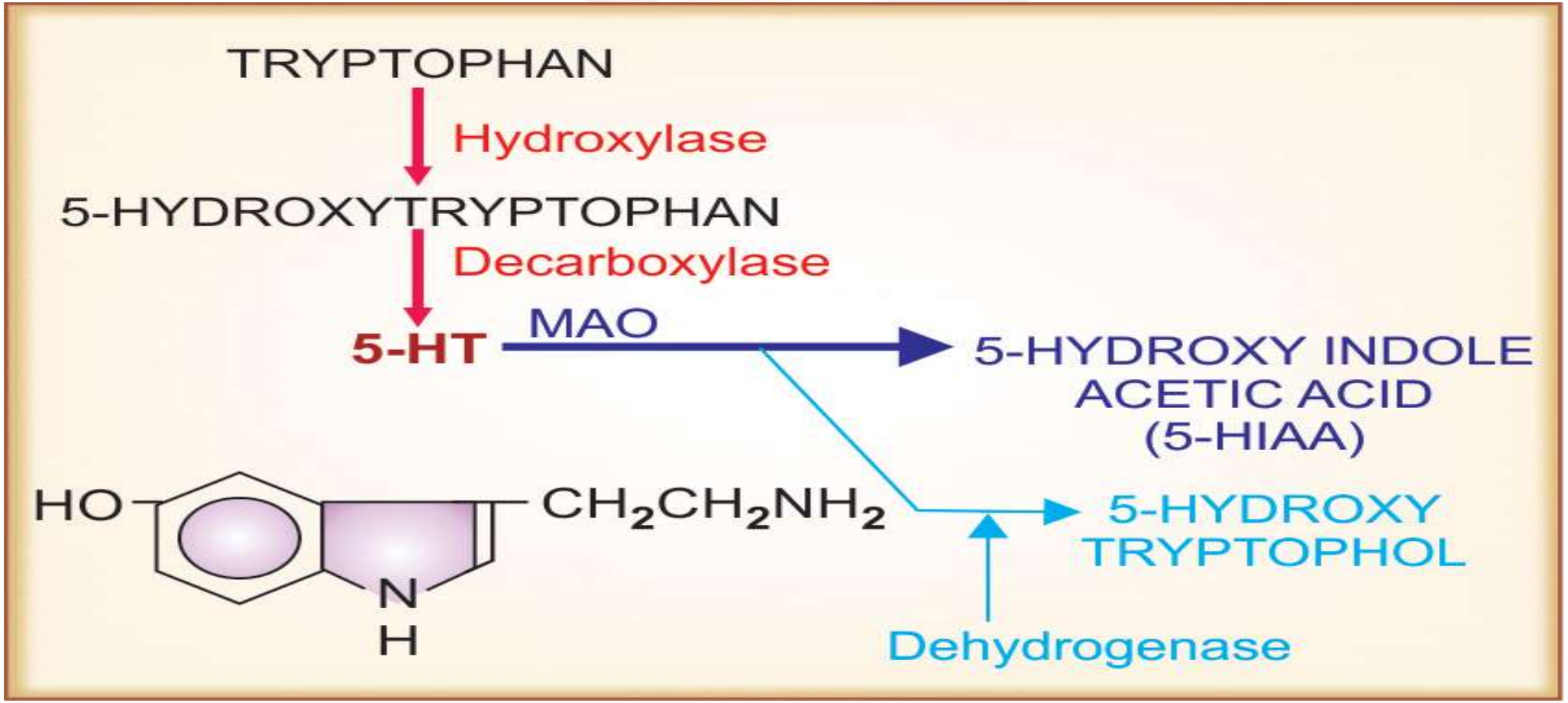
- Teratogenic

5HT (Serotonin)

A monoamine (*5-hydroxytryptamine*) neurotransmitter biochemically derived from tryptophan.

These are basically vasoconstrictor substances.

SYNTHESIS, STORAGE AND DESTRUCTION



Serotonin Receptors:

Receptor	Type and mechanism	Location	actions	Agonist or antogonist
5-HT 1	Gi Dec in c AMP	•CNS (raphe nuclei and hippocampus) •cranial blood vessels	•Dec 5HT release •Constriction of cranial BVs. •Decreased release of peptides from nerve endings.	•Buspirone •Triptans (selective 5 HT 1b/1d) •Ergonemetrin (partial antagonist)
5-HT 2	Gq Increased IP3 and DAG •Platelets •Smooth muscles •Cerebral cortex (2a)	•Platelets •Smooth muscles •Cerebral cortex (2a) •Fundus of stomach(2B) •Choroid(2c)	•Platelet aggregation. •Smooth muscle contraction •(+) of neurons •CSF production. •2A antagonistkatanserin, cyproheptadine	•2A antagonistkatanserin, cyproheptadine, atypical antipsychotics. •2A/2C antagonistmethysergide
5-HT 3	Ligand gated Na and K channels	•CTZ •NTS •Parasymp nerve terminal (GIT)	•Vomiting •Peristalsis •Stimulate neurons	•Odansetron, granisetron (5-HT 3 antagonsits)
5-HT 4	Gs Increased c AMP	•GIT •CNS	•Peristalsis •Enchance gut secretions.	•Agonists – renzapride, metoclopramide, prucalopride.

Pharmacological Actions:

CVS-

- 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.

Visceral smooth muscles-

- 5-HT is a potent stimulator of g.i.t.

Glands

- 5-HT inhibits gastric secretion

Platelets

- changes in shape of platelets

PATHOPHYSIOLOGICAL ROLES

- *Neurotransmitter*
- *Precursor of melatonin*
- *Neuroendocrine function*
- *Nausea and vomiting*
- *Migraine*
- *Haemostasis*
- *Variant angina*

5-HT ANTAGONISTS

Cyproheptadine- 5-HT2A

Ketanserin- 5-HT2

Clozapine- 5-HT2A/2C

Risperidone- 5-HT2A

Ondansetron- 5-HT3

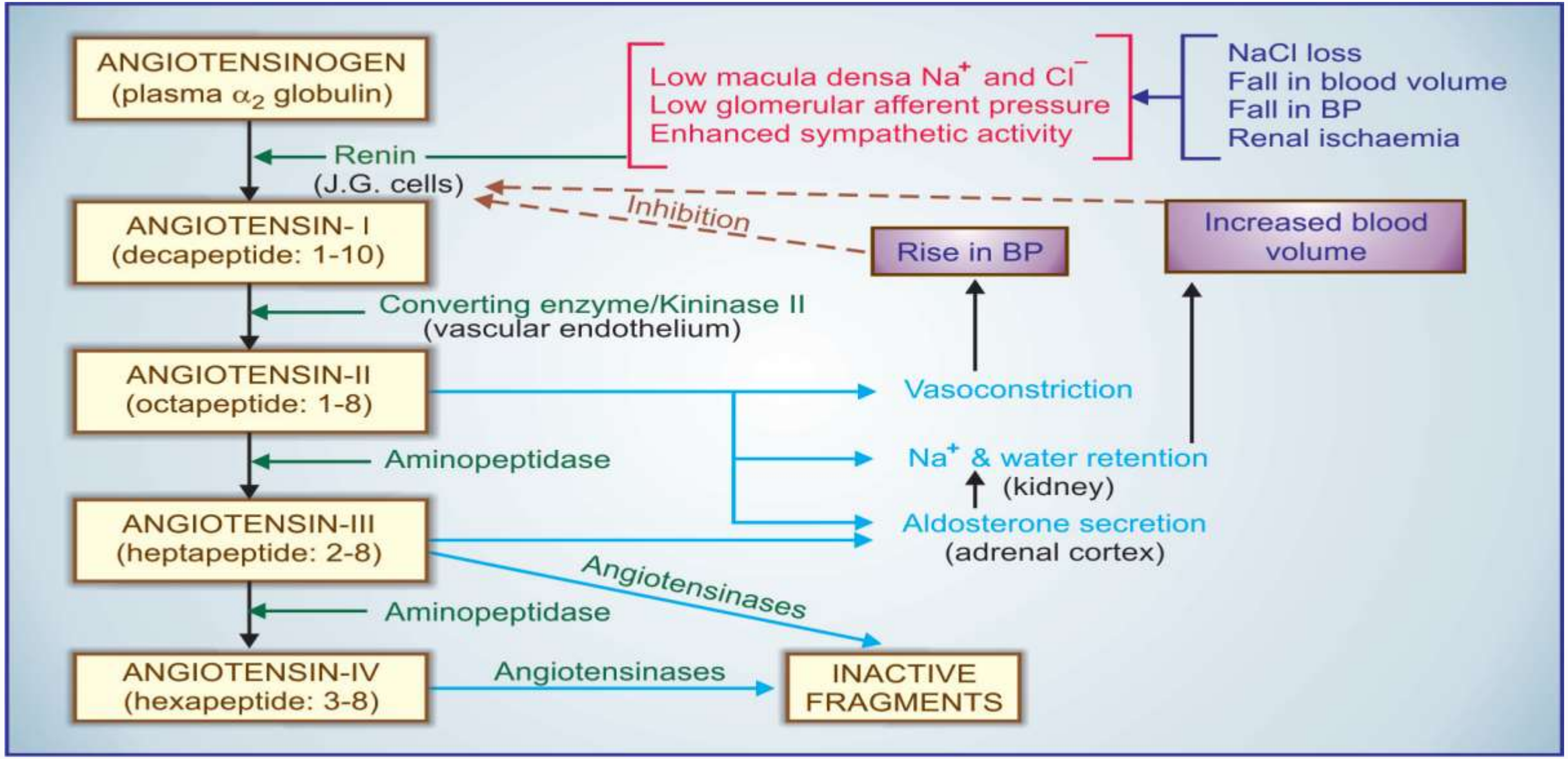
Angiotensin

It is an octapeptide derivative local hormone involved mainly in Blood Pressure regulation and Fluid balnce in the body.

Active form is Angiotensin II.

It generally discussed in RAAS System (Renin Angiotensin Aldosterone system)

Angiotensin Synthesis and action Pathway:



ANGIOTENSIN RECEPTORS:

There are two subtypes AT1 and AT2 receptors.

Both are G-Protein coupled Receptors.

Location:

Found in the heart, blood vessels, kidney, adrenal cortex, lung and brain and mediates the vasoconstrictor effects.

Mechanism of action:

Receptors attached with Gq/11 and Gi/o

Activation of phospholipase C

Cytosolic Ca2+ Increase

stimulation of protein kinase C

Effects of angiotensin II

- Vasoconstriction (CVS)
- Aldosterone synthesis and secretion(Adrenal Cortex)
- vasopressin secretion
- vascular smooth muscle cells proliferation, decreased renal blood flow,
- Renal renin inhibition (Kidney)
- Modulation of central sympathetic nervous system activity (CNS)

Bradykinin

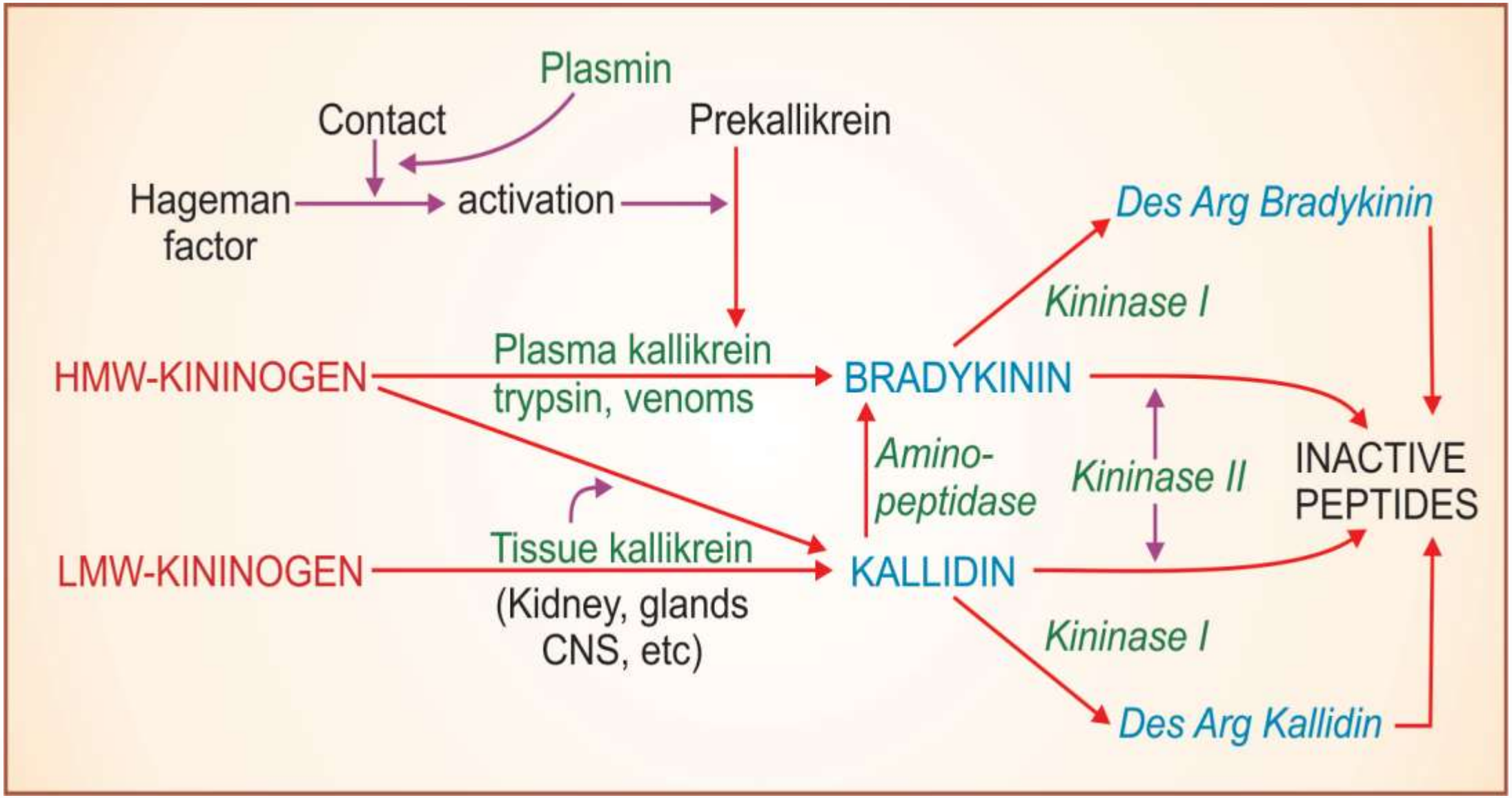
It is a plasma kinin.

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.

Synthesis and Metabolism:



Pharmacological actions:

CVS:

- more potent vasodilators than ACh and histamine.
- The dilatation is mediated through endothelial NO and PGI2 generation, and
- Larger arteries, most veins and vessels with damaged endothelium are constricted through direct action on the smooth muscle.

Smooth muscle: contraction of intestine and bronchoconstriction.

Neurones: stimulate nerve endings that transmit pain and produce a burning sensation.

Kidney: increase renal blood flow and facilitate salt and water excretion.

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,competative antagonist of the bradykinin 2 receptor used inmanagement of Heriditary angioedema

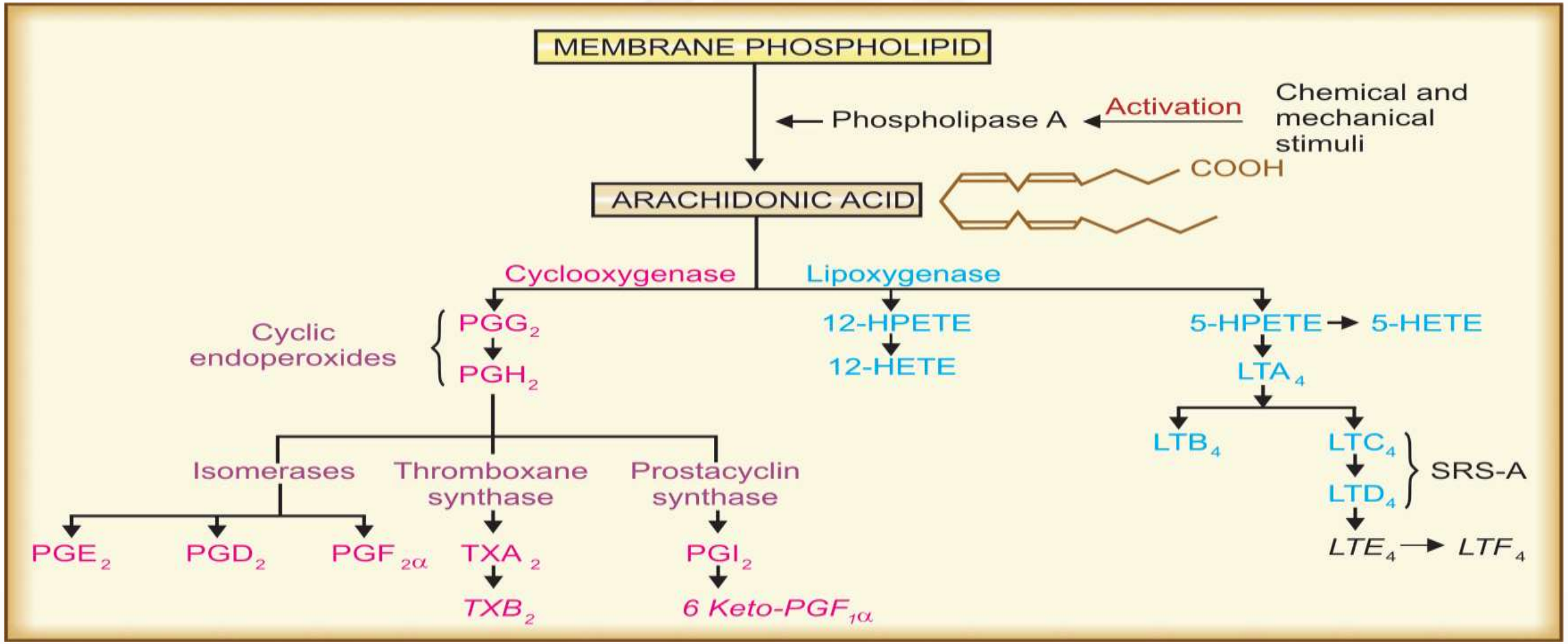
PROSTAGLANIDS , THROMBOXANES and LEUKOTRIENES

These are collectively called as Eicosanoids which means 20 carbon unsaturated fatty acids derivatives.

These all are Inflammatory mediators.

These all are produced via Arachidonic acid Pathway from the membrane phospholipids during inflammatory responses.

Biosynthesis:



Prostaglandins Receptors:

Prostaglandins ligate is a sub-family of cell surface seven-transmembrane receptors, G-protein-coupled receptors.

Type of PG Receptor Function	Type of PG Receptor Function	Type of PG Receptor Function
PGI2	IP EP1 EP2	Vasodilation, Inhibits platelet aggregation, bronchodilatation Bronchoconstriction, GI tract smooth muscle contraction Bronchodilatation, GI tract smooth muscle relaxation, vasodilatation
PGE2	EP2 EP3	Bronchodilatation, GI tract smooth muscle relaxation, vasodilatation ↓ Gastric acid secretion ↑ gastric mucus secretion uterus contraction (when pregnant) GI tract smooth muscle contraction ↑ autonomic neurotransmitters ↑ platelet response to their agonists and ↑ atherothrombosis in vivo
PGF2α	FP	Uterus contraction bronchoconstriction

Clinical use of Prostaglandins:

Therapeutic Abortion- PGE1 Misoprostol with mifepristone (a progesterone antagonist)

Gastric cytoprotection (Gastric ulcer)- PGE1 Misoprostol

Impotence- PGE1 Alprostadil

Maintenance of patent Ductus arteriosus- PGE1 Alprostadil

Pulmonary Hypertension-PGI2 epoprostenol (Flolan)

Leukotrienes

Leukotrienes are fatty molecules of the immune system that contribute to inflammation in asthma and allergic rhinitis.

Leukotrienes are produced in the body from arachidonic acid by the enzyme 5-lipoxygenase.

- Examples: LTA4, LTB4, LTC4, LTD4, LTE4, and LTF4, LTC4, LTD4 and LTE4

Functions

- Leukotrienes are involved in asthmatic and allergic reactions and act to sustain inflammatory reactions.
- Leukotrienes are very important agents in the inflammatory response
- Leukotrienes contribute to 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 antagonist

- Leukotriene inhibitors (or modifiers), such as montelukast, zafirlukast and zileuton, are used to treat those diseases.

- There are two main approaches to block the actions of leukotrienes:

1. Inhibition of the 5-lipoxygenase pathway
2. Antagonism of cysteinyl-leukotriene type 1 receptors

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Thank You