AUTACOIDS

INTRODUCTION

- AUTACOIDS auto=self akos=healing/remedy
- Local Hormones

CLASSIFICATION

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

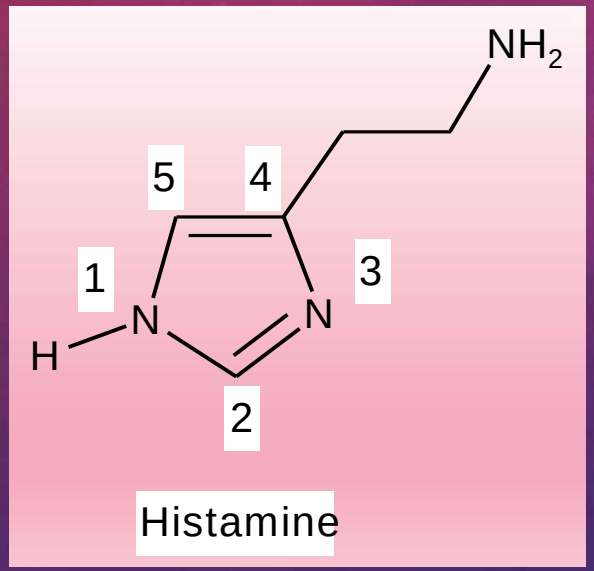
FUNCTIONS

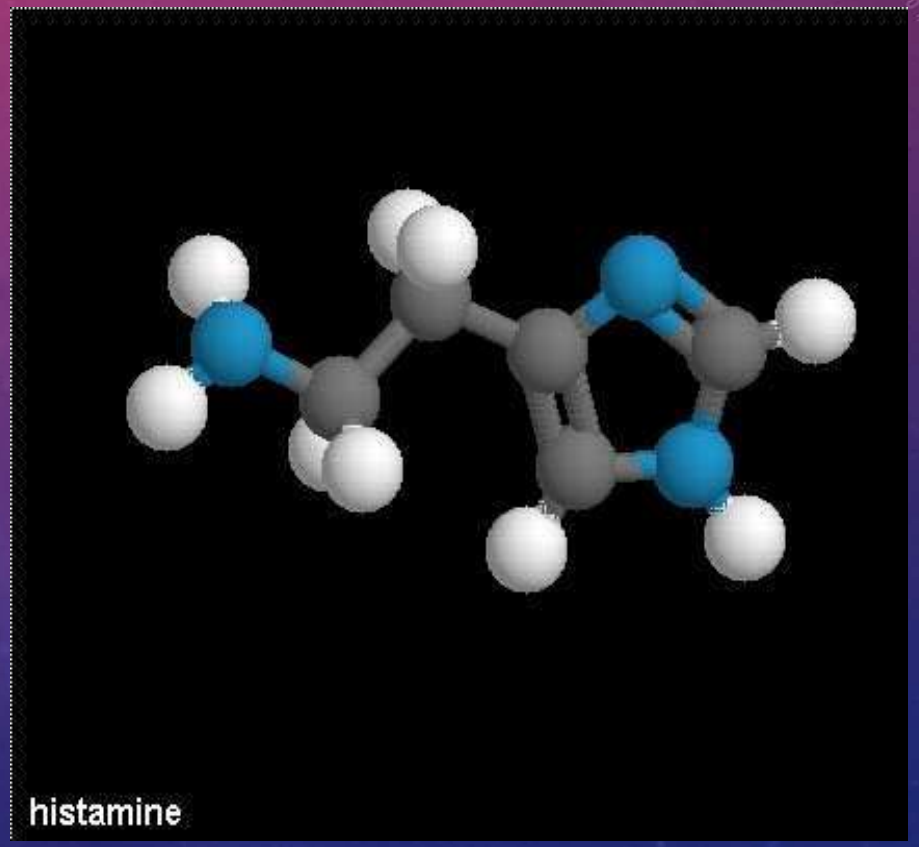
- Physiological
- Pathophysiological (Reaction to injuries)
- Transmission and Modulation

AMINE AUTACOIDS

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

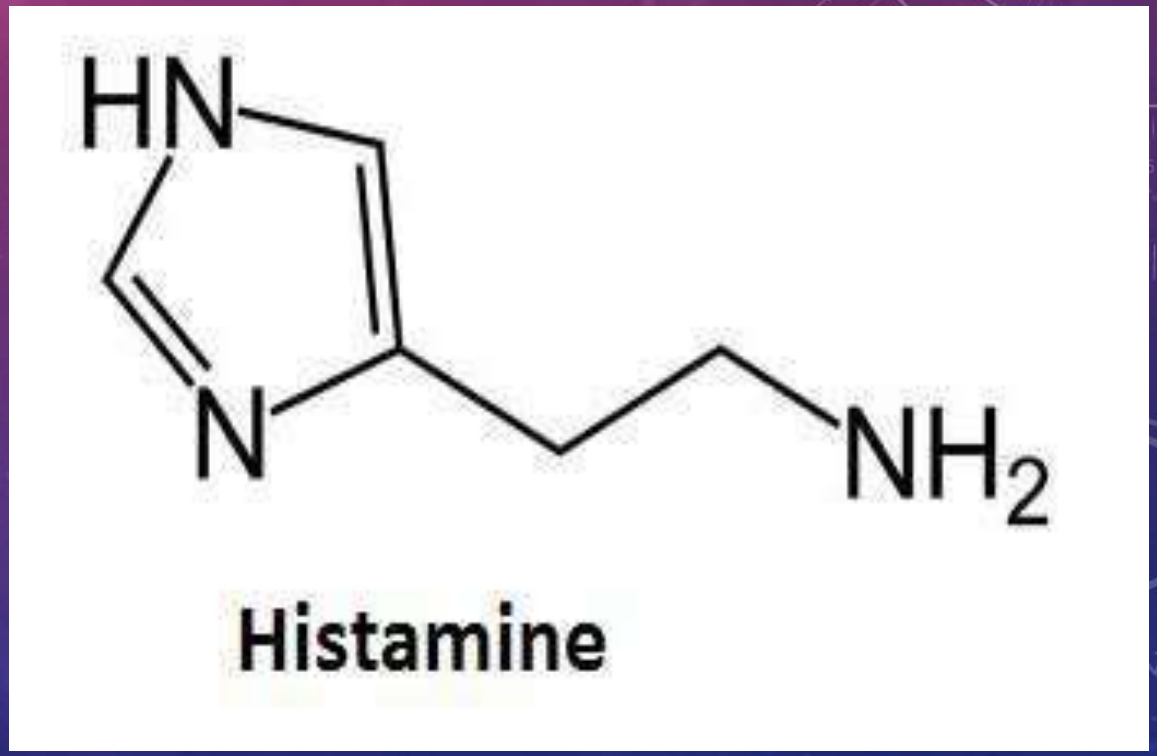
HISTAMINE





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.



Histamine

SITES OF HISTAMINE RELEASE

1) Mast cell site: Pulmonary tissue (mucosa of bronchial tree)

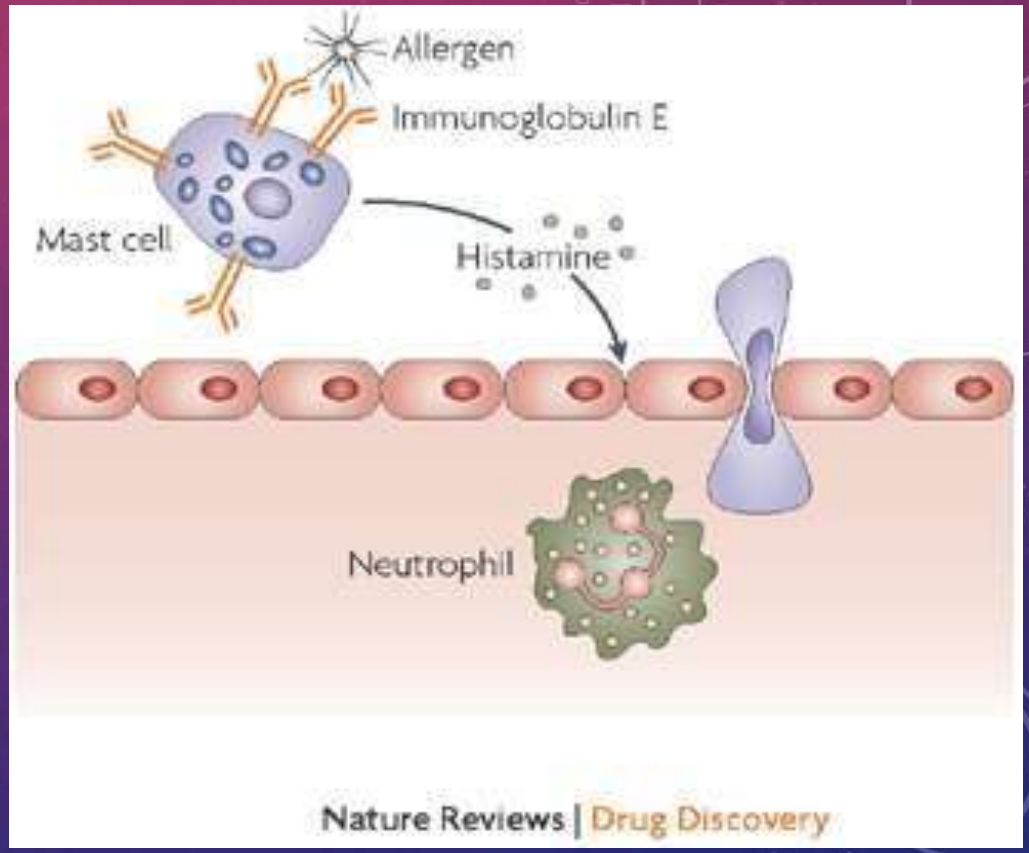
- Skin
- GIT(intestinal mucosa)
- Conc. Of histamine is particularly high in these tissues

2) Non-mast cell sites:

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

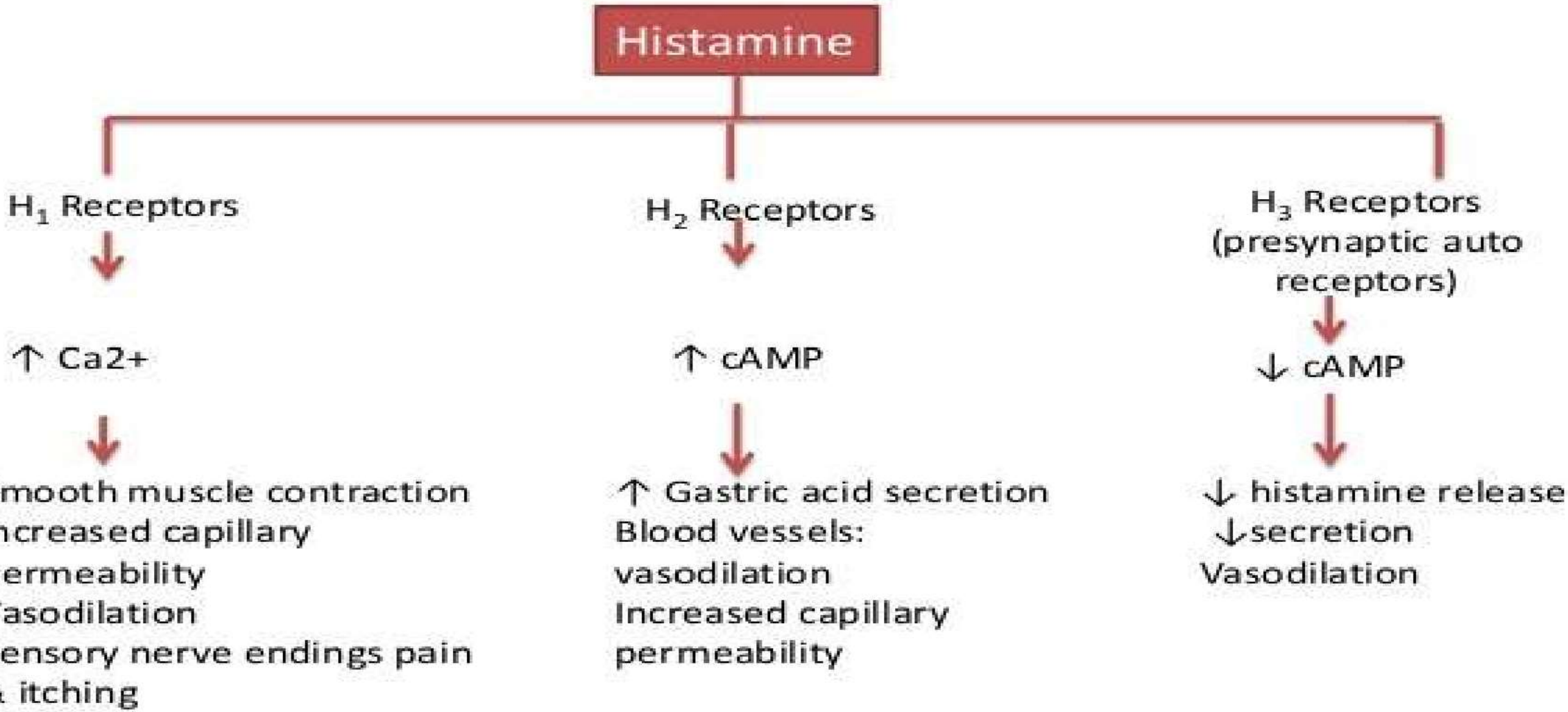
MECHANISM OF RELEASE

- 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.



SYNTHESIS AND DEGRADATION:

Mechanism of Action of Histamine



receptor	mechanism	Location and function	agonists	antagonsits
H 1	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.	2 methyl histamine, 2-pyridyl ethylamine,	Mepyramine, chlorphenaramine,
H 2	Gs type Increase in c AMP. Phosphorylation 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	Thioperamide, impromidine, ciproflaxacin
H 4	G I Dec in c AMP	Mediate mast cell chemotaxis		Thioperamide

ORGAN SYSTEM EFFECTS OF HISTAMINE

NERVOUS SYSTEM	Powerful stimulation of sensory endings, especially nerve mediating pain and itching
CARDIOVASCULAR SYSTEM	Decrease in systolic and diastolic blood pressure
BRONCHIAL SMOOTH MUSCLE	Increase in sense of bronchoconstriction
GASTROINTESTINAL TRACT	Contraction of intestinal smooth muscle, large doses of histamine may cause diarrhea
UTERUS	Abortion in pregnant women
SECRETORY TISSUE	Stimulation of gastric acid, pepsin & intrinsic factor. Increased secretion in the small and large intestine

HISTAMINE ANTAGONISTS

H1 receptor antagonist

1) Sedative (first generation) antihistamines: Highly lipid soluble and easily enters into the CNS:

a) Potent and marked sedative:

• Promethazine (phenergan) *widely used* • Diphenhydramine Dimenhydrinate

b) Potent and moderate sedative:

• Chloryclizine • Chlorpheniramine • Tetrahydeoxy carboline

c) Less potent and less sedative: • Mepyramine • Pheniramine(avil) 25.

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

• Cetrizine • Terfenadine • Astemizole • Loratadine • Ketotifen • Cyclizine

Indication of H_1 blockers

1)Dermatitis of all types.
2)Allergic reaction :Urticaria,Rhinitis,Conjunctivitis and
3)Anaphylactic shock
4)Anti-motion sickness: diphenhydramine
5)Anti-emetic:Cyclizine,Meclizine,Doxylamine (in pregnancy)
6) Anti-parkinsonism: Diphenhydramine is used.
7) Preanesthetic medication
8) As sedative agent: Promethazine
9)Cough depressant.
10)Otitis media.
11)common cold.

ROLE IN ALLERGY:

- Allergies are caused by a hypersensitivity reaction of the antibody class IgE (which are located on mast cells in the tissues and basophils in the blood)
- When an allergen is encountered, it binds to IgE, which excessively activates the mast cells or basophils, leading them to release massive amounts of histamines
- These histamines lead to inflammatory responses ranging from runny nose to anaphylactic shock
- If both parents have allergies, you have a 70% chance of having them, if only one parent does, you have a 48% chance (American Academy of Asthma, Allergies and Immunology, Spring 2003)

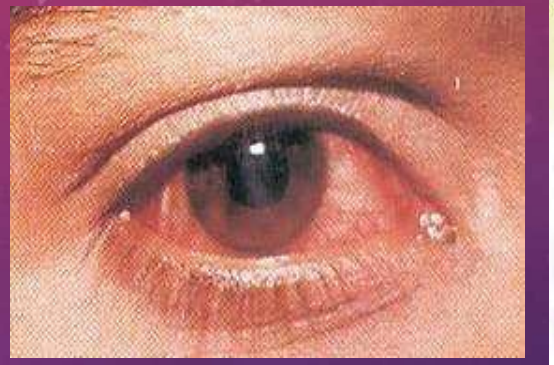
HISTAMINE EFFECTS ACCORDING TO PLASMA HISTAMINE CONCENTRATION

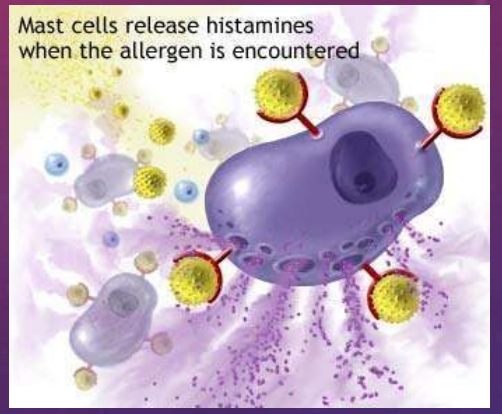
Histamine Clinical effect concentration in ng/ml:

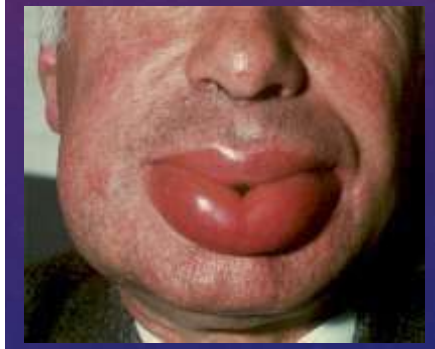
- 0–1 Reference
- 1–2 ↑ Gastric acid secretion ↑ Heart rate
- 3–5 Tachycardia, headache, flush, urticaria
- 6–8 ↓ Arterial pressure
- 7–12 Bronchospasm ≈100 Cardiac arrest

ADVERSE EFFECTS OF HISTAMINE RELEASE

- Itching, Urticaria
- Flushing
- Hypotension
- Tachycardia
- Bronchospasm
- Angioedema
- Wakefulness
- Increased acidity (Gastric acid secretion)







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 headche.

USES:

- No therapeutic value
- Occasionally used in some diagnostic tests:
  - Testing gastric acid secretion.
  - Diagnosis of phechromocytoma.
  - 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:
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  - 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

PHARMACEUTICAL PRODUCTS

First generation anti-histamines for allergies (active ingredients and brand names):

DRUG	**BRAND**
Brompheniramine –	**Dimetane**
Chlorpheniramine –	**Chlor-Trimeton**
Diphenhydramine –	**Benadryl**

Second generation anti-histamines for allergies (active ingredients and brand names):

Loratadine	–	**Claritin**
Cetirizine	–	**Zyrtec**

Dosage:

Cetirizine (Zyrtec): Tablet - 5-10 mg orally once a day depending upon symptom severity. Syrup – 5 mg/ 5 mL

Loratadine (Claritin, Tavist), Brompheniramine (Dimetane): Tablet – 10mg once daily for adults, 5 mg once daily for children 2 to 5 years.

Chlorpheniramine (Chlor-Trimeton) – 4 mg orally every 4 - 6 hrs; sustained-release: 8 or 12 mg orally every 8 - 12 hours. Maximum dose: 24 mg/day.

Diphenhydramine (Benadryl): 25 mg to 50 mg (1-2 capsules) per day for adults and children above 12 years; for children 6 -12 years of age – 25 mg (1 capsule)

Side effects – drowsiness especially in case of first generation antihistamines, restlessness, nervousness, upset stomach, dry mouth, irritability, difficulty urinating and sometimes blurred vision.

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 selectivitiy: 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 H_1-blockers

Drug	Route and duration of action	Important features
Cetirizine	PO, 12–24 h	• H_1 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	• 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	• 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	• H_1 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.

Preanesthic 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 Ca2+ from endolymph into the vestibular sensory cells.
  - Beneficial effects have been reported in Méniére's disease and other types of vertigo.
- Parkinsonism
  - Promethazine and diphenhydramine are used for the treatment of driug induced parkinsonism.
- *Cough*
  - *Antihistaminics like chlorpheniramine,* diphenhydramine and promethazine are used.
  - no selective cough suppressant action, afford symptomatic relief by sedative and anticholinergic property .

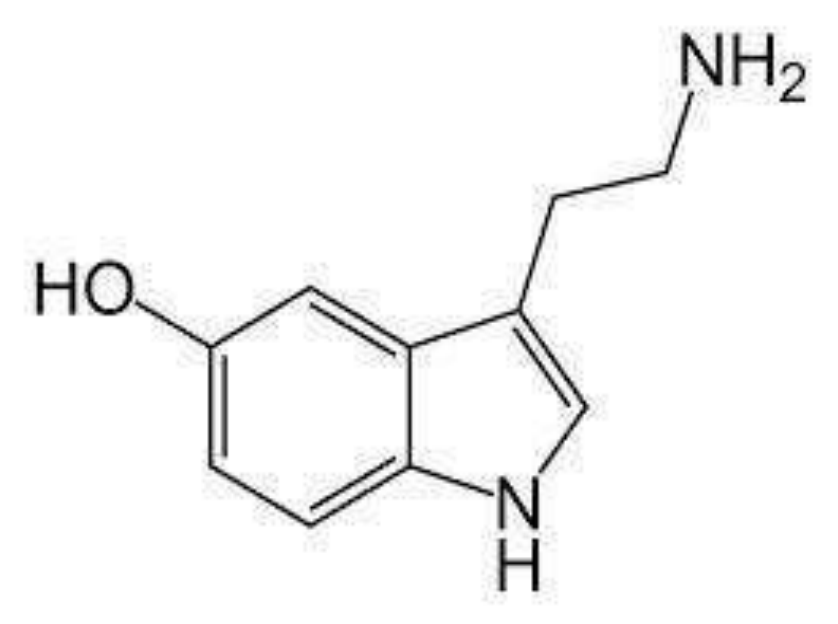
- *As sedative, hypnotic, anxiolytic*
  - *Antihistamines* with CNS depressant action have been used as sedative and to induce sleep, especially in children.

ADVERSE EFFECTS:

- Common
  - Sedation, drowsiness, lack of concentration, headache, fatigue, weakness, 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
- Allegric reactions can occur

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

SEROTONIN OR 5-HYDROXYTRYPTAMINE (5-HT)



- Molecular formula : $C_{10}H_{12}ON_2$
- 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.
- The remainder is 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, 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.

IMPORTANCE OF SEROTONIIN

Serotonin is believed to play a central role in:

- Modulation of vasoconstriction
- Anger
- Aggression
- Body temperature
- Mood
- Sleep
- Sexual desire
- appetite
- Stimulation of vomiting reflex
- Memory and Learning

SOURCES

- Found abundantly in the gut and blood plasma, but it can not enter the brain.
- Meat and Banana are the direct sources of serotonin.
- Main source: L-tryptophan, an amino acid, which is found in proteins. So proteins are the main sources of serotonin:

➢ Meat, eggs, milk, fishes

➢ Pulses

- Enough calcium, magnesium and oxygen are also needed for serotonin production.
- Vitamin B6 also promotes its production.

High level of serotonin:

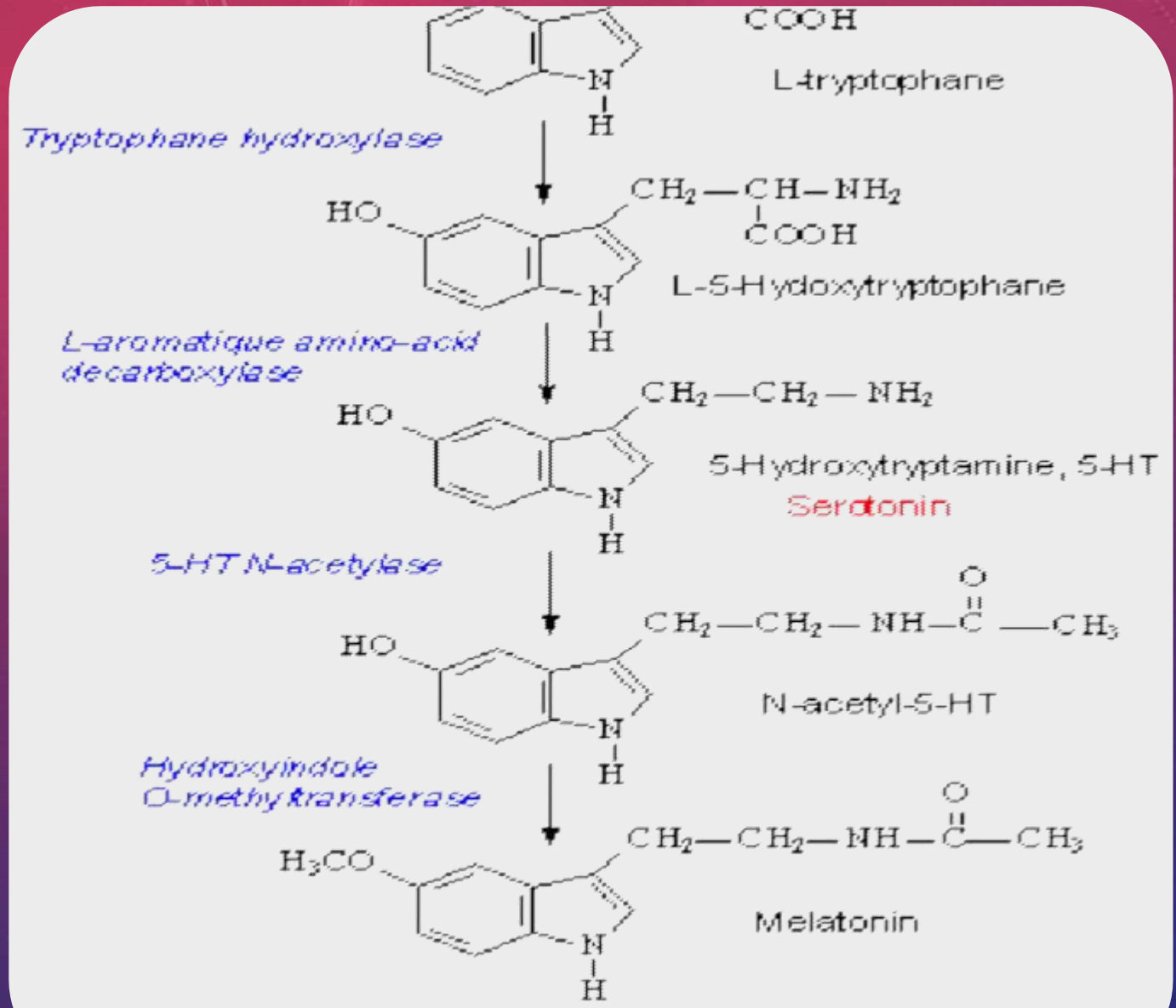
- Obsessive-compulsive disorders e.g. compulsive hand-washing
- Pulmonary vasoconstriction causing an acute or chronic pulmonary hypertension
- Cardiac fibrosis

Low levels of Serotonin:

- Irritability, Irrational emotions, Sudden unexplained tears, Sleep disturbances, Depression, Suicidal tendencies
- When we have enough Serotonin we have: Emotional stability, Reduces aggression, Sleep cycle, Appetite control

SYNTHESIS

- Serotonin is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of two enzymes:
  - Tryptophan hydroxylase (TPH)
  - Amino acid decarboxylase (DDC)


COOH
L-tryptophane
Tryptophane hydroxylase
HO
CH2—CH—NH2
COOH
L-5-Hydoxytryptophane
L-aromatique amino-acid decarboxylase
CH2—CH2—NH2
5-Hydroxytryptamine, 5-HT
Serotonin
5-HT N-acetylase
O
CH2—CH2—NH—C—CH3
N-acetyl-5-HT
Hydroxyindole O-methyltransferase
H3CO
Melatonin

5-HT RECEPTORS

- Receptors are divided into 7 types: 5-HT_1 to 5-HT_7
- 5-HT_1 group consist of 5 receptor subtypes:

- 5-HT_{1A}
- 5-HT_{1B}
- 5-HT_{1D}
- 5-HT_{1E}
- 5-HT_{1F}

5-HT_{1A} RECEPTORS

- Most extensively distributed of all 5-HT receptors.
- In CNS, these receptors are present in high density in cerebral cortex, and raphe nucleus.
- Involved in inhibition of discharge of neurons, regulation of production of behaviour and eating.
- Play an important role in the emergence of anxiety.
- Agonists: Buspiron, Ergotamine, Yohimbine and Antagonists are Alprenolol, Pindolol, Propranolol.

5-HT_{1B} RECEPTORS

- Present in CNS where they induce presynaptic inhibition and behavioural effects
- Exhibit vascular effects as well, such as pulmonary vasoconstriction
- Agonists: Ergotamine, Dihydroergotamine, Zolmitriptan
- Antagonists: Yohimbine, Propranolol, Pindolol

- The Clinical significance of 5-HT_{1D} receptor is still largely unknown
- The function of 5-HT_{1E} receptor is unknown but it is hypothesized that they are involved in regulation of memory
- 5-HT_{1F} receptor has a possible role in vascular contraction. Distribution in brain appears limited

5-HT_2 RECEPTORS

- This class has 3 subtypes:

- 5-HT_{2A}
- 5-HT_{2B}
- 5-HT_{2C}

Receptors	Effcets & Function	Agonist	Antagonist
5-HT2A	CNS: Anxiety, Imagination, Learning, Perception SM: Contraction Platelet: Aggregation	Yohimbine	Aripiprazole, Clozapine, Olanzapine, Trazodone
5-HT2B	CNS: Anxiety GIT: GI Motility	Norfenfluramine	Agomelatine
5-HT2C	CNS: Mood, Sleep, Anxiety	--	Clozapine, Olanzapine

5-HT_3 Receptors:

- With the exception of the 5-HT_3 receptor, a ligand- gated ion channel, all other serotonin receptors are G protein-coupled receptors that activate an intracellular second messenger cascade to produce an excitatory or inhibitory response
- The 5-HT_3 receptor antagonist suppress vomiting and nausea by inhibiting serotonin binding to the 5-HT_3 receptors

5-HT_4 Receptors:

- Found on CNS and Myenteric neurons.
- Prucalopride (brand name Resolor, developed by Johnson & Johnson) is a drug acting as a selective, high affinity 5-HT_4 receptor agonist which targets the impaired motility associated with chronic constipation, thus normalising bowel movements

5-HT_5 Receptors:

- Pharmacological functions of these receptors are unknown. Based on their localization, it has been speculated that they may be involved in motor control, anxiety, learning, adaptive behaviour and brain development.

5-HT_6 Receptors:

- The exact clinical significance of these receptors remain still unclear. Selective antagonist of this type of serotonin receptor have an impact on behaviour and seem to improve the spatial memory of laboratory animal

5-HT_7 Receptors:

- Expressed abundantly in the vessels and are responsible for persistent vasodilation. 5-HT_7 receptors are also expressed in CNS and in smooth muscles (in GIT tract).

SEROTONIN SYNDROOME

- Extremely high levels of serotonin can cause a condition known as Serotonin Syndrome, with toxic and potentially fatal effects.

- Drugs used to treat SEROTONIN SYNDROME

➢ Non–specific blocking agents: Methysergide, Cyproheptadine

➢ Beta blockers: Propranolol, Pindolol

➢ Benzodiazepines: Lorazepam, Diazepam, Clonazepam

MIGRAINE

- 5-HT_1 agonists (e.g. Sumatriptan) are first- line therapy for severe migraine and are effective on cluster headache.
- Many other different drugs are also used in migraine such as Propranolol, valproic acid. NSAIDs such as aspirin and ibuprofen are often helpful in controlling the pain of migraine.

VOMITING

- 5-HT_3 receptors participate in the vomiting reflex.
- Particularly important in vomiting caused by anti cancer drugs. Ondansetron is the prototypical 5-HT_3 antagonist. Important in the prevention of nausea and vomiting associated with surgery and cancer chemotherapy.

DEPRESSION

- A class of drugs, such as fluoxetine or sertraline, that inhibit the uptake of serotonin by neurons of the central nervous system are primarily used in the treatment of depression and obsessive compulsive disorder known as SSRIs
- A few of them are: Citalopram (Cipram, Seropram), Fluoxetine (Prozac, Evorex), Paroxetine (Paxil, Seroxat, Aropax), Sertraline (Zoloft, Lustral, Serlain)

LIPID DERIVED AUTACOIDS

- Biologically active derivatives of 20 C-atoms polyunsaturated essential fatty acids that are major lipid derived autacoids.
- Derived from arachidonic acids.
- Two major types of eicosanoids-
  - ✓ Prostaglandins (PGs)
  - ✓ Leukotrienes (LTs)
- The eicosanoids are important local hormones and they may act as circulating hormones as well.
- In the body PGs, TXs and LTs are all derived from eicosa (Referring to 20c atoms) tri, tetra, penta enoic acids; so that they are collectively called eicosanoids.

PROSTAGLANDINS

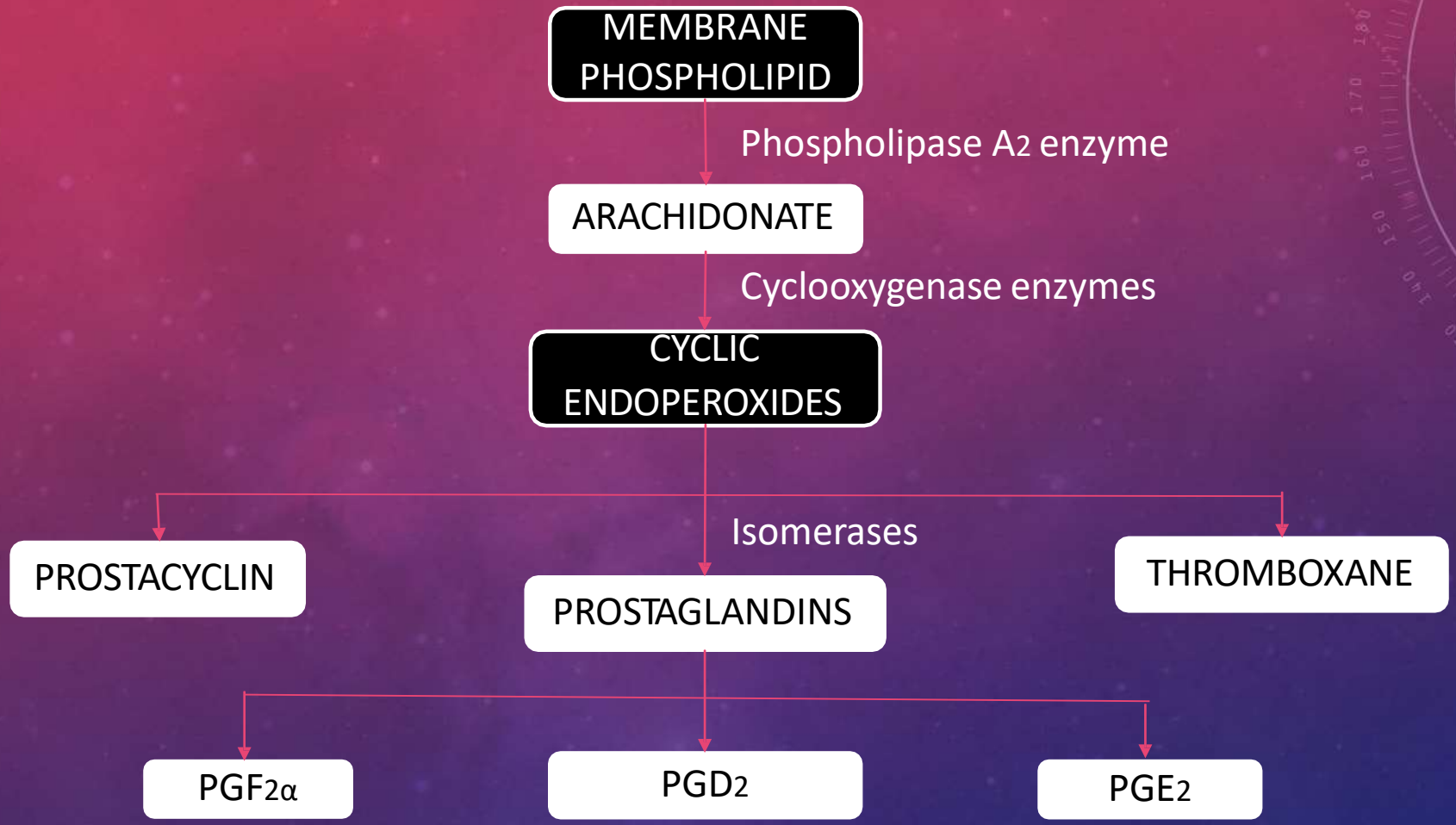
WHAT ARE PROSTAGLANDINS ?

- Group of hormone-like lipid compounds
- Derived enzymatically from fatty acids
- Perform important functions in the animal body
- 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).

RELEASE OF PROSTAGLANDINS FROM THE CELL

mediated by a specific transporter, namely the multidrug resistance protein 4 (MRP4, ABCC4), a member of the ATP-binding cassette transporter superfamily. Whether MRP4 is the only transporter releasing prostaglandins from the cells is still unclear.

BIOSYNTHESIS AND ACTIONS OF PROSTAGLANDINS



Actions:

- Bronchoconstriction
- Myometrial Contraction

Actions

- Inhibits Platelet aggregation
- Vasodilator

Actions

- Vasodilator
- Hyperalgesic

PHARMACOLOGICAL ACTIONS

1) Regulation of Blood Pressure

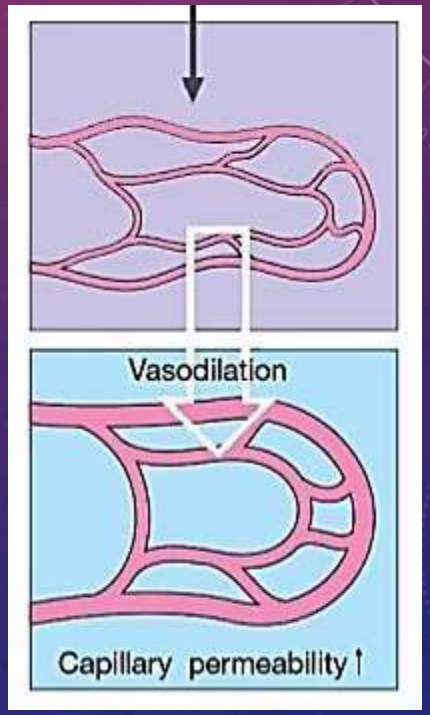
PGE_2 and PGI_2 are vasodilators in vascular beds

↓

Increased blood flow and decreased peripheral resistance

↓

Lower BP



2) Inflammation

PGE_1 and PGE_2 induce the symptoms of Inflammation

(redness, swelling etc.) due to vasodilation.

3) Reproduction

PGE_2 AND $PGF_{2\alpha}$ causes contraction of Uterine

smooth muscles in pregnant women.

4) Pain and Fever

It acts on thermoregulatory centre of hypothalamus

to produce fever

Pyrogens (fever producing agents) promotes PG synthesis

↓

Formation of PGE2 in hypothalamus

↓

Fever associated with Pain

5) Regulation of Gastric secretion

- PG inhibits Gastric secretion
- PG stimulate pancreatic secretion and increase the motility of the intestine leads to diarrhoea

6) Influence on immune system

PGE decreases immunological functions of B and T lymphocytes

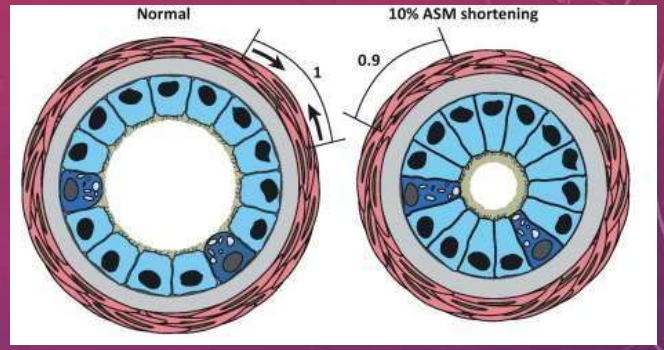
7) Effect on respiratory function

PGEs causes bronchial smooth muscle relaxation

PGFs causes bronchial smooth muscle constriction

thus

PGE and PGF oppose the action of each other in the lungs

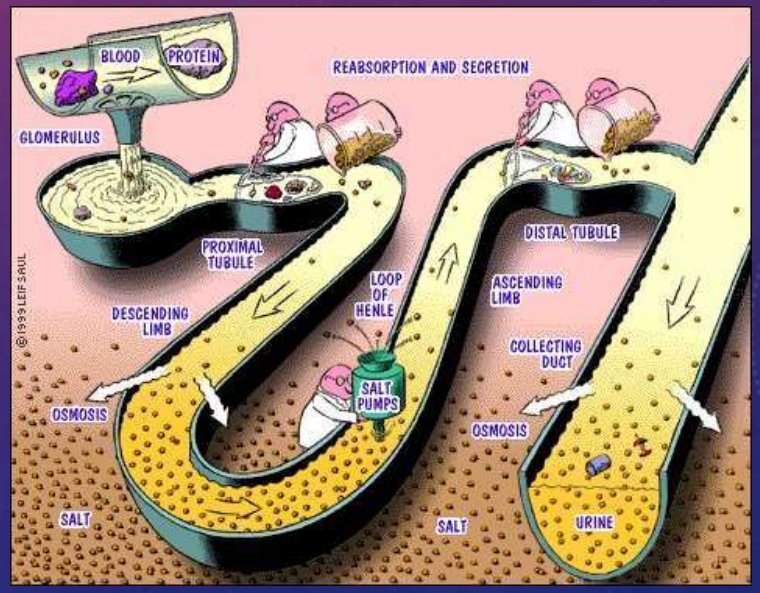


8) Influence on renal functions

PG increases Glomerular Filtration rate

thus

Promotes Urine Output



9) Effect on platelet aggregation

- PGI2 inhibits platelet aggregation

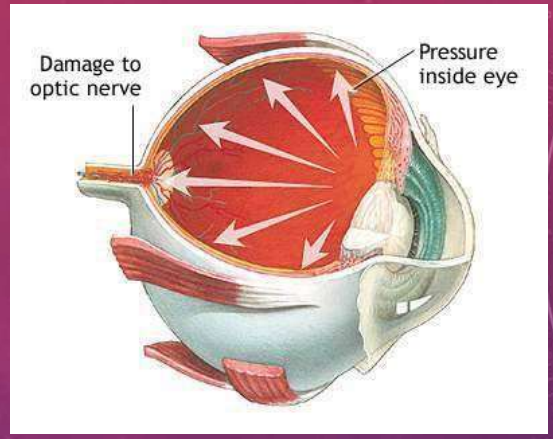
•Thromboxane and PGE2 promotes platelet aggregation and blood clotting which might lead to thrombosis

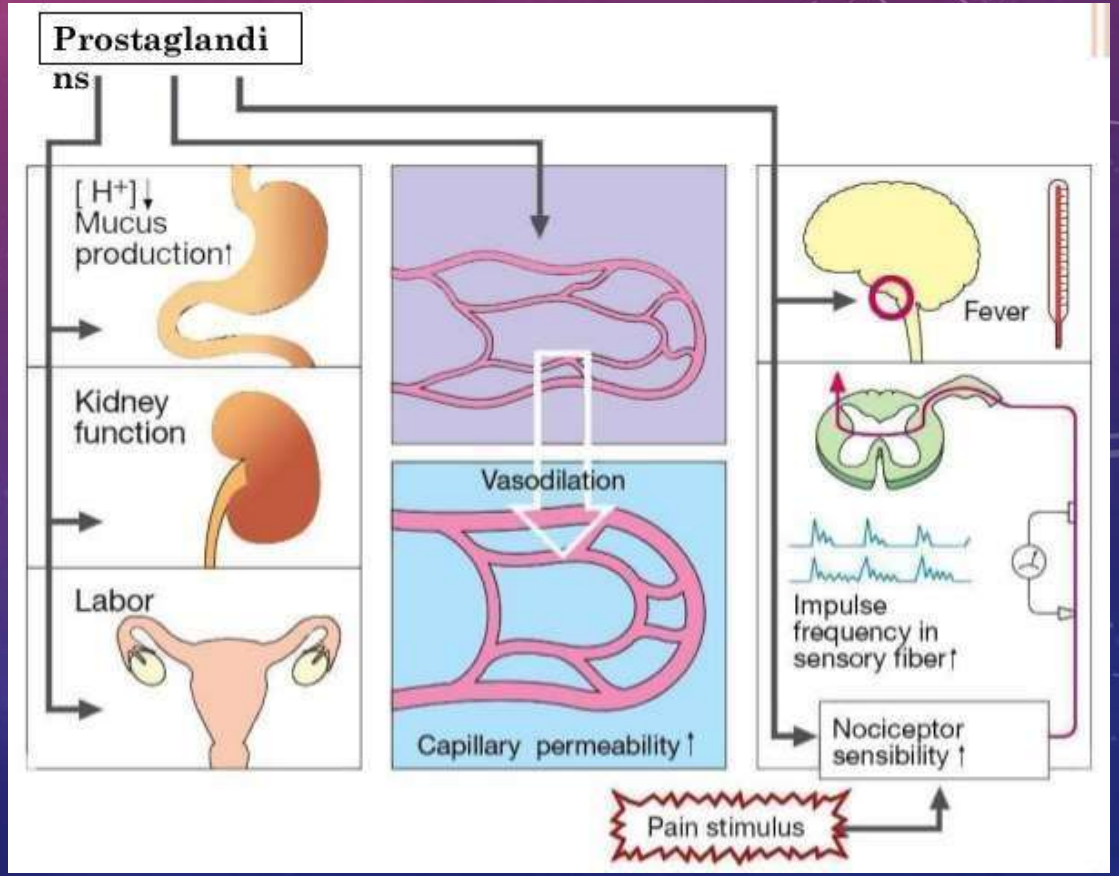
10) Eye

It decreases intraocular pressure

11) CNS

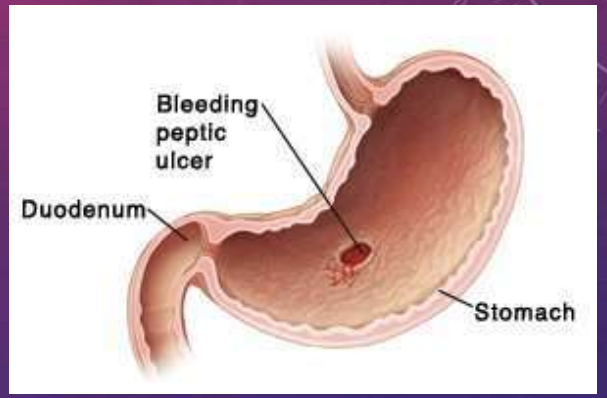
- regulate hormones
- sensitize spinal neurons to pain

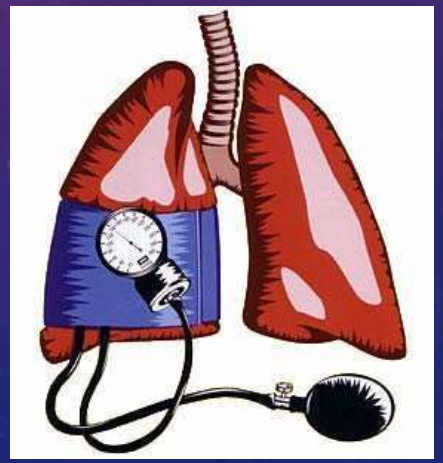




USES

1. Obstetrics (Abortion, Induction of Labour, Cervical Ripening, Postpartum Haemorrhage)
2. Peptic Ulcer
3. Glaucoma
4. Erectile dysfunction
5. Primary Pulmonary hypertension



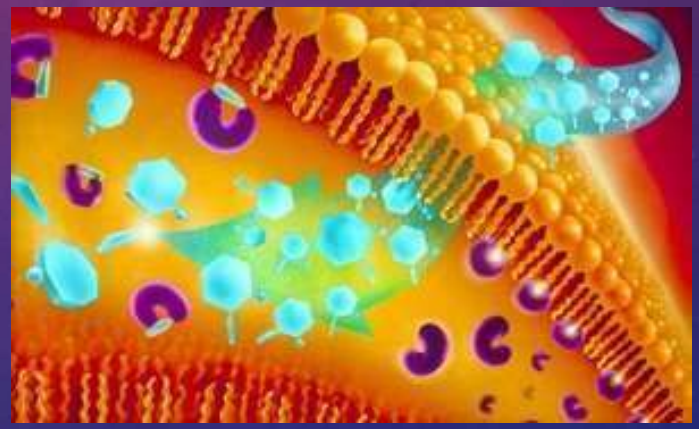


WHAT HAPPENS WHEN THERE IS INCREASE IN PROSTAGLANDIN SECRETION ?

- **Conditions** such as arthritis, heavy menstrual bleeding and painful menstrual cramps and certain types of cancer including colon and breast cancer might happen.
- **Anti-inflammatory drugs** - aspirin and ibuprofen, work by blocking the action of the cyclooxygenase enzymes and so reduce prostaglandin levels.

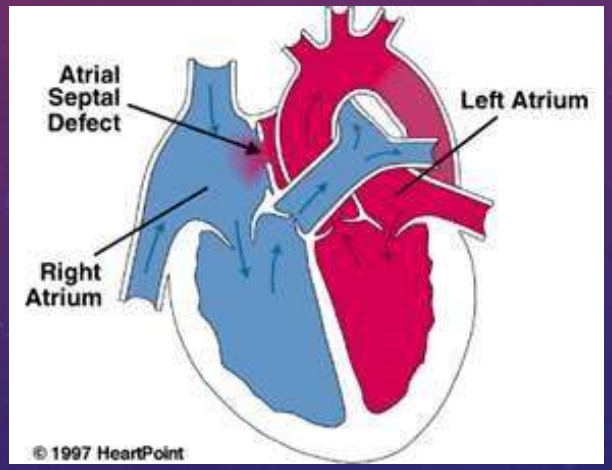
Example:

Mechanism of action of the drug aspirin.



WHAT HAPPENS IF TOO FEW PROSTAGLANDINS ?

- Manufactured prostaglandins can be used to increase prostaglandin levels in the body under certain circumstances.
- Administration of prostaglandins can induce labour at the end of pregnancy or abortion in the case of an unwanted pregnancy.
- They can also be used to treat stomach ulcers, glaucoma and congenital heart disease in new born babies.



DRUG	USE	BRAND
Misoprostol	Abortion, PPH , Peptic Ulcer	Mifenac (East west Pharma), Safeguard (Pulse Pharma)
Methotrexate	Abortion, PPH	Folitrax (IPCA), Caditrex (Cadila), Oncotrex (Sun)
Carboprost	Abortion, PPH	Deviprost (Dr. Reddy), Caboprost (Neon labs)
Enprostil	Peptic Ulcer	Aciphex (Eisai Pharma)
Epoprostenol	Platelet aggregation, Pulmonary hypertension	Flolan, Veletri
Latanoprost	Glaucoma	9PM (Cipla), Ioptama (Cadila)
Bimatoprost	Glaucoma	Careprost (Sun pharma)
Travoprost	Glaucoma	Lupitros (Lupin)
Tadalafil	Erectile Dysfunction	36 hours (Cadila), Forzest (Ranbaxy)
Sildenafil	Pulmonary hypertension	Alsigra (Alembic), Cavetra (Ranbaxy)

LEUKOTRIENES

- Leukotrienes are so named because they were first obtained from leukocytes (leuko) and conjugated double bonds

TYPES OF LEUKOTRIENES

- **Cysteinyl leukotrienes:** LTC_4, LTD_4, LTE_4 and LTF_4
- **LTB_4**
  - synthesized *in vivo* from LTA_4 by the enzyme LTA_4 hydrolase
  - primary function is to recruit neutrophils to areas of tissue damage, though it also helps promote the production of inflammatory cytokines by various immune cells.
- **LTG_4**
  - a metabolite of LTE_4 in which the cysteinyl moiety oxidized to an alpha-keto-acid (i.e. the cysteine has been replaced by a pyruvate)

FUNCTIONS OF LEUKOTRIENES

- Act principally on a subfamily of G protein coupled receptors
- May also act upon peroxisome proliferator-activated receptors
- Involved in asthmatic and allergic reactions and act to sustain inflammatory reactions; several leukotriene receptor antagonists
- Very important agents in the inflammatory response
- LTB_4 have a chemotactic effect on migrating neutrophils, and as such help to bring the necessary cells to the tissue

USED IN PROPHYLAXIS

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

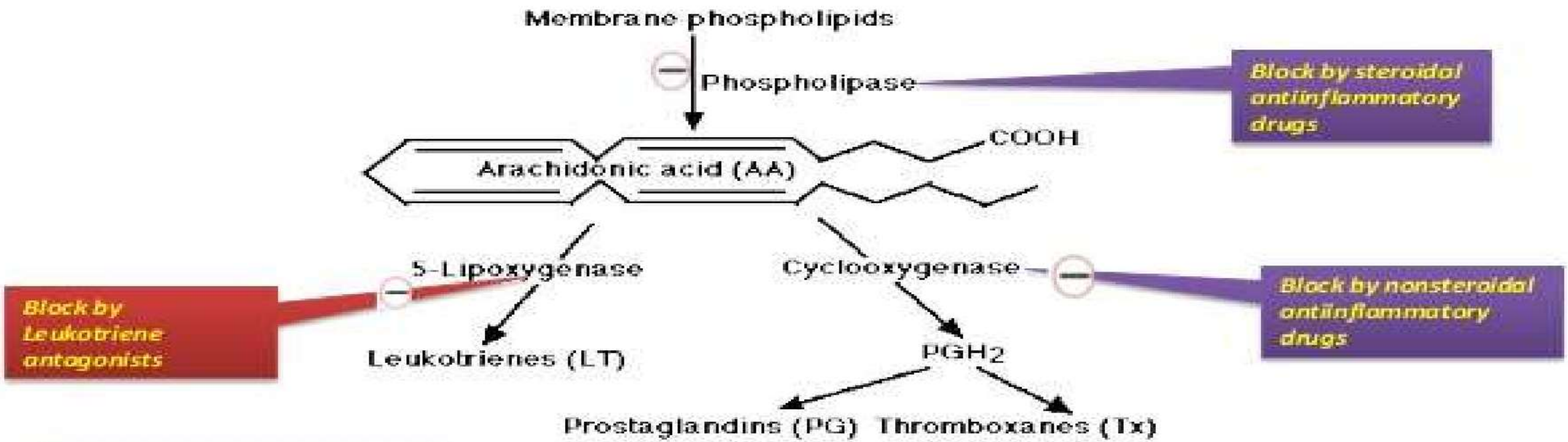
CHRONIC ASTHMA

- Asthma is a common inflammatory illness
- Characterized by airway inflammation and hyper responsiveness to stimuli that produce bronchoconstriction
- These stimuli include cold air, exercise, a wide variety of allergens and emotional stress–
  - Extrinsic asthma: It is mostly episodic, less prone to status asthmaticus
  - Intrinsic asthma: It tends to be perennial, status asthmaticus is more common

Leukotriene antagonists

Cont.,

- **Mechanism of action of leukotriene antagonist, antiinflammatory drugs**



Bronchoconstriction, Inflammation, increased mucus

Bronchoconstriction, Inflammation, Pain

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)

Zafirlukast (Accolate) :

- Avoid at mealtimes
- Take 1 hour before or 2 hours after meals
- Dose:
  - Age >11 years old: 20 mg bid
  - Child 7-11 years old: 10 mg bid

Montelukast (Singulair):

- Dose:
  - Adults: 10 mg
  - Child age 6 to 14 years: 5 mg
  - Child age 2-5 years: 4 mg

Zileuton (Zyflo):

- Indicated in age only 12 and over
- Dose: 600 mg orally four times daily
- Hepatotoxicity in 5%
- Drug interactions: Warfarin, theophylline, Propranolol

EFFICACY

- Modestly effective for maintenance management
- Inhaled Steroids are preferred over leukotriene agents
- Used as adjunctive therapy in Asthma
- Benefit may be limited to patients with the 5-LO and LTC4 polymorphisms

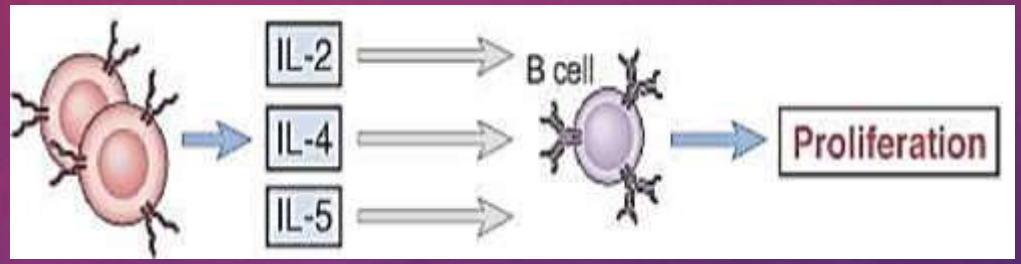
INTERLEUKINS

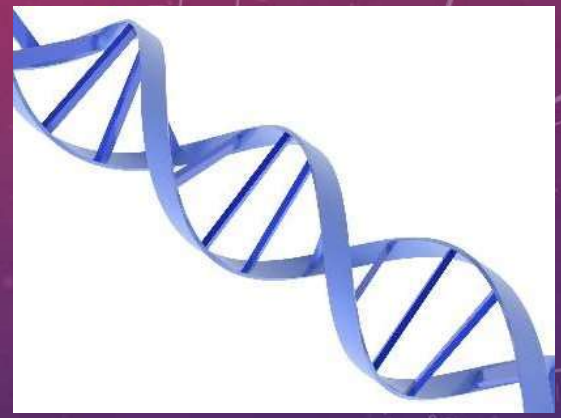
WHAT ARE INTERLEUKINS?

- Interleukins are a group of cytokines (secreted proteins and signalling molecules) that were first seen to be expressed by white blood cells (leukocytes).
- Assigned to each family based on sequence homology and receptor chain similarities or functional properties.
- The majority of interleukins are synthesized by helper CD4 T lymphocytes, as well as through monocytes, macrophages, and endothelial cells.
- They promote the development and differentiation of T and B lymphocytes, and hematopoietic cells.

Action:

- Pleiotropic effect
- Redundancy



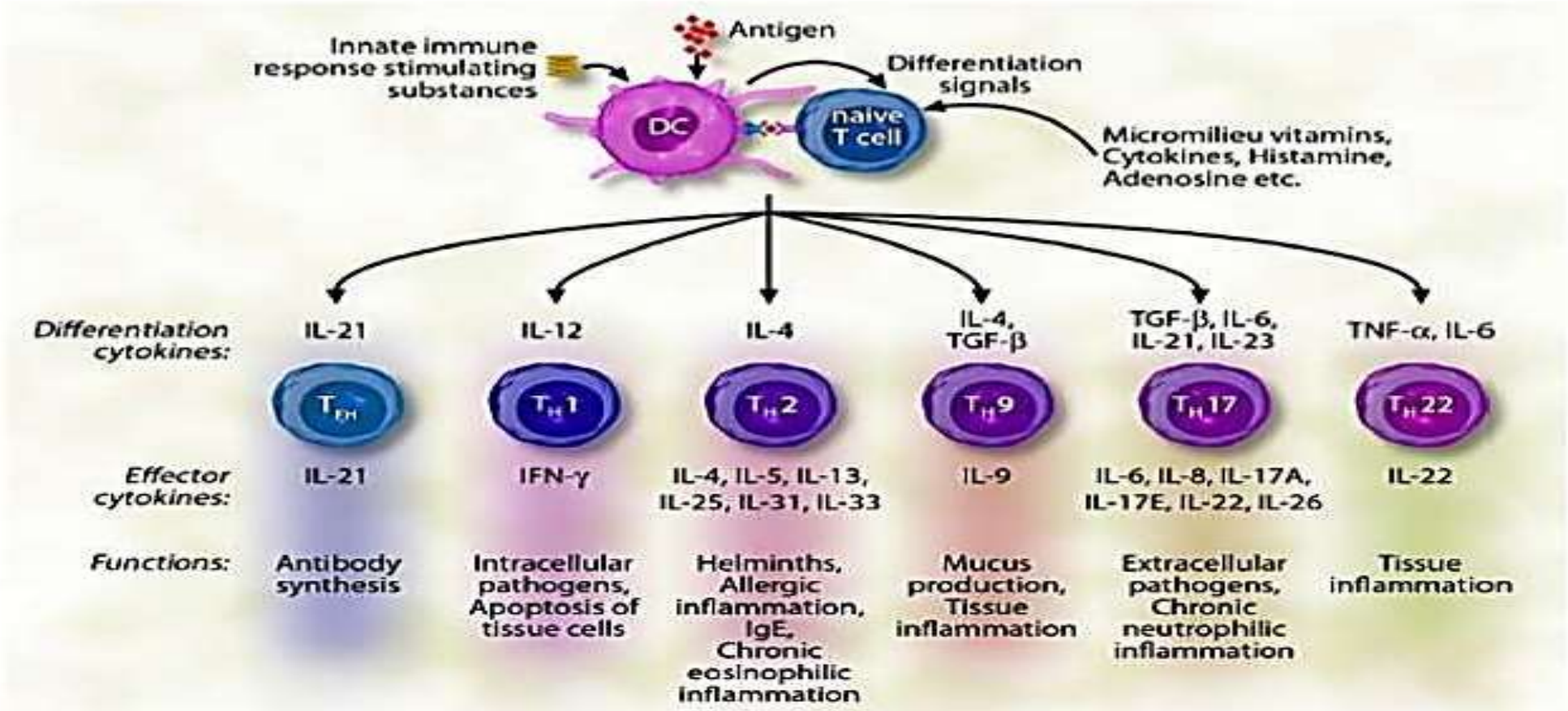


Classification:

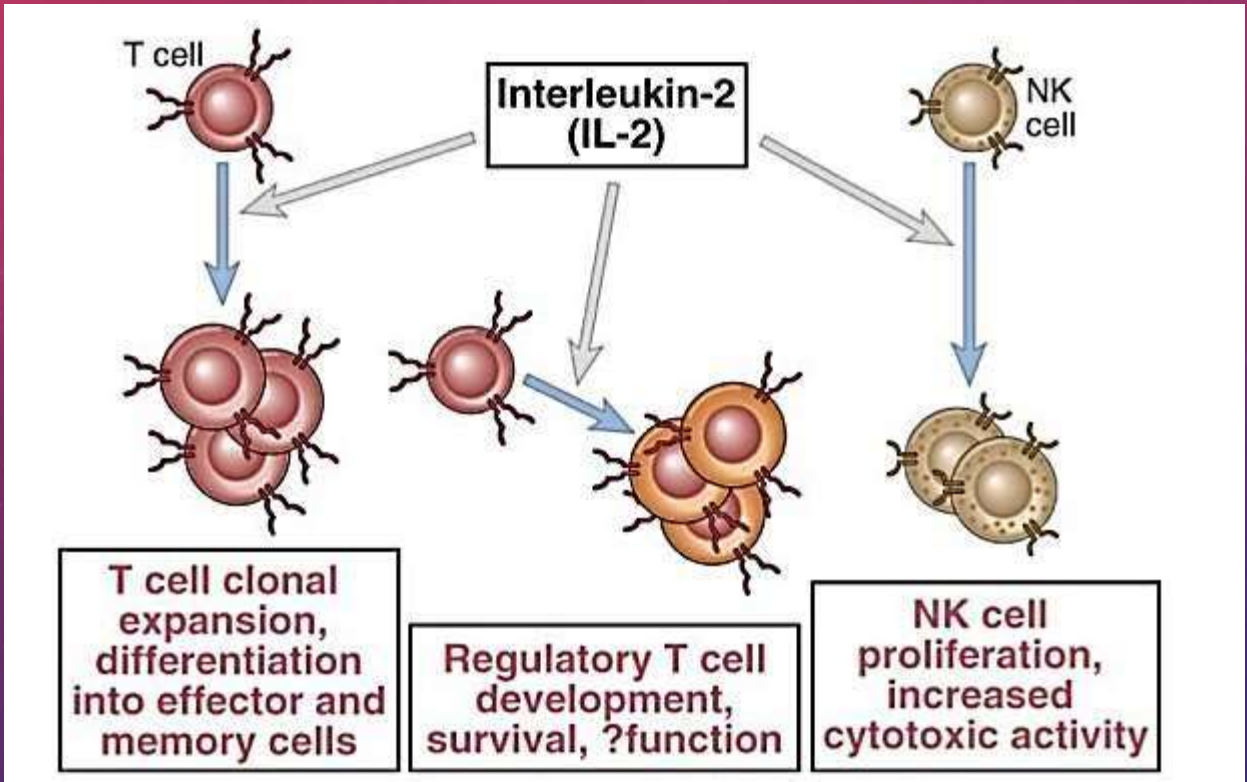
- Type 1 cytokines (Hematopoietin)
- Type 2 cytokines (Interferon)

RELEASE OF INTERLEUKINS

Antigen presentation by DCs to naive T cells and other factors induces the T cells to produce ils and differentiate into TH1, TH2, TH9, TH17, TH22, or follicular TH (TFH) cells. These T-cell subsets can promote different types of inflammatory responses on the basis of their respective cytokine profiles, responses to chemokines, and interactions with other cells.



HOW DOES IT FUNCTION ?



Biological Actions of IL-2 : IL-2 stimulates the proliferation and differentiation of T & B lymphocytes and NK CELLS. IL-2 also functions to inhibit immune responses (against self antigens) by its effect on regulatory T cells.

LIST OF HUMAN INTERLEUKINS

NAME	SOURCE	TARGET CELLS	FUNCTION
IL-1	MACROPHAGES, B CELLS, MONOCYTES, DENDRITIC CELLS	T HELPER CELLS	CO-STIMULATION
		B CELLS	MATURATION & PROLIFERATION
		NK CELLS	ACTIVATION
		MACROPHAGES, ENDOTHELIUM, OTHER	INFLAMMATION, SMALL AMOUNTS INDUCE ACUTE PHASE REACTION, LARGE AMOUNTS INDUCE FEVER
IL-2	TH1-CELLS	ACTIVATED T CELLS AND B CELLS, NK CELLS, MACROPHAGES, OLIGODENDROCYTES	STIMULATES GROWTH AND DIFFERENTIATION OF T CELL RESPONSE. CAN BE USED IN IMMUNOTHERAPY TO TREAT CANCER OR SUPPRESSED FOR TRANSPLANT PATIENTS. HAS ALSO BEEN USED IN CLINICAL TRIALS (ESPIRIT. STALWART) TO RAISE CD4 COUNTS IN HIV POSITIVE PATIENTS.
IL-3	ACTIVATED T HELPER CELLS, MAST CELLS, NK CELLS, ENDOTHELIUM, EOSINOPHILS	HEMATOPOIETIC STEM CELLS	DIFFERENTIATION AND PROLIFERATION OF MYELOID PROGENITOR CELLS TO E.G. ERYTHROCYTES, GRANULOCYTES
		MAST CELLS	GROWTH AND HISTAMINE RELEASE
IL-4	TH2 CELLS, JUST ACTIVATED NAÏVE CD4+ CELL, MEMORY CD4+ CELLS, MAST CELLS, MACROPHAGES	ACTIVATED B CELLS	PROLIFERATION AND DIFFERENTIATION, IGG1 AND IGE SYNTHESIS. IMPORTANT ROLE IN ALLERGIC RESPONSE (IGE)
		T CELLS	PROLIFERATION
		ENDOTHELIUM	

IL-5	**TH2 CELLS, MAST CELLS, EOSINOPHILS**	**EOSINOPHILS**	**PRODUCTION**
		B CELLS	DIFFERENTIATION, IGA PRODUCTION
IL-6	MACROPHAGES, TH2 CELLS, B CELLS, ASTROCYTES, ENDOTHELIUM	ACTIVATED B CELLS	DIFFERENTIATION INTO PLASMA CELLS
		PLASMA CELLS	ANTIBODY SECRETION
		HEMATOPOIETIC STEM CELLS	DIFFERENTIATION
		T CELLS, OTHERS	INDUCES ACUTE PHASE REACTION, HAEMATOPOIESIS, DIFFERENTIATION, INFLAMMATION
IL-7	BONE MARROW STROMAL CELLS AND THYMUS STROMAL CELLS	PRE/PRO-B CELL, PRE/PRO-T CELL, NK CELLS	DIFFERENTIATION AND PROLIFERATION OF LYMPHOID PROGENITOR CELLS, INVOLVED IN B, T, AND NK CELL SURVIVAL, DEVELOPMENT, AND HOMEOSTASIS, ↑PROINFLAMMATORY CYTOKINES
IL-8 OR CXCL8	MACROPHAGES, LYMPHOCYTES, EPITHELIAL CELLS, ENDOTHELIAL CELLS	NEUTROPHILS, BASOPHILS, LYMPHOCYTES	NEUTROPHIL CHEMOTAXIS

IL-9	**TH2 CELLS, SPECIFICALLY BY CD4+ HELPER CELLS**	**T CELLS, B CELLS**	**POTENTIATES IGM, IGG, IGE, STIMULATES MAST CELLS**
IL-10	MONOCYTES, TH2 CELLS, CD8+ T CELLS, MAST CELLS, MACROPHAGES,B CELL SUBSET	MACROPHAGES	CYTOKINE PRODUCTION
		B CELLS	ACTIVATION
		MAST CELLS	
		TH1 CELLS	INHIBITS TH1 CYTOKINE PRODUCTION (IFN-Γ, TNF-B, IL-2)
		TH2 CELLS	STIMULATION
IL-11	BONE MARROW STROMA	BONE MARROW STROMA	ACUTE PHASE PROTEIN PRODUCTION, OSTEOCLAST FORMATION
IL-12	DENDRITIC CELLS, B CELLS, T CELLS,MACROPHAGES	ACTIVATED T CELLS	DIFFERENTIATION INTO CYTOTOXIC T CELLS WITH IL-2, ↑ IFN-Γ, TNF-A, ↓ IL-10
		NK CELLS	↑ IFN-Γ, TNF-A
IL-13	ACTIVATED TH2 CELLS, MAST CELLS,NK CELLS	TH2-CELLS, B CELLS, MACROPHAGES	STIMULATES GROWTH AND DIFFERENTIATION OF B CELLS (IGE), INHIBITS TH1-CELLS AND THE PRODUCTION OF MACROPHAGE INFLAMMATORY CYTOKINES (E.G. IL-1, IL-6), ↓ IL-8, IL-10, IL-12

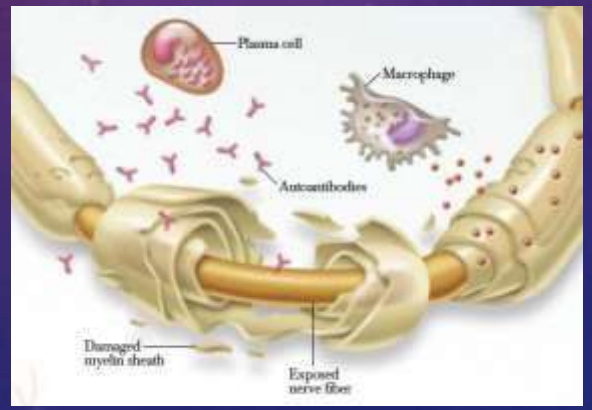
IL-14	**T CELLS AND CERTAIN MALIGNANT B CELLS**	**ACTIVATED B CELLS**	**CONTROLS THE GROWTH AND PROLIFERATION OF B CELLS, INHIBITS IG SECRETION**
IL-15	MONONUCLEAR PHAGOCYTES (AND SOME OTHER CELLS), ESPECIALLY MACROPHAGES FOLLOWING INFECTION BY VIRUS(ES)	T CELLS, ACTIVATED B CELLS	INDUCES PRODUCTION OF NATURAL KILLER CELLS
IL-16	LYMPHOCYTES, EPITHELIAL CELLS, EOSINOPHILS, CD8+ T CELLS	CD4+ T CELLS (TH-CELLS)	CD4+ CHEMO ATTRACTANT
IL-17	T HELPER 17 CELLS (TH17)	EPITHELIUM, ENDOTHELIUM, OTHER	OSTEOCLAST GENESIS, ANGIOGENESIS, ↑ INFLAMMATORY CYTOKINES
IL-18	MACROPHAGES	TH1 CELLS, NK CELLS	INDUCES PRODUCTION OF IFNΓ, ↑ NK CELL ACTIVITY
IL-20	ACTIVATED KERATINOCYTES AND MONOCYTES		REGULATES PROLIFERATION AND DIFFERENTIATION OF KERATINOCYTES

IL-21	ACTIVATED T HELPER CELLS, NKT CELLS	ALL LYMPHOCYTES, DENDRITIC CELLS	COSTIMULATES ACTIVATION AND PROLIFERATION OF CD8+ T CELLS, AUGMENT NK CYTOTOXICITY, AUGMENTS CD40-DRIVEN B CELL PROLIFERATION, DIFFERENTIATION AND ISOTYPE SWITCHING, PROMOTES DIFFERENTIATION OF TH17 CELLS
IL-22	T HELPER 17 CELLS (TH17)		PRODUCTION OF DEFENSINS FROM EPITHELIAL CELLS. ACTIVATES STAT1 ANDSTAT3 AND INCREASES PRODUCTION OF ACUTE PHASE PROTEINS SUCH ASSERUM AMYLOID A, ALPHA 1-ANTICHYMOTRYPSIN AND HAPTOGLOBIN IN HEPATOMA CELL LINES
IL-23	MACROPHAGES, DENDRITIC CELLS		MAINTENANCE OF IL-17 PRODUCING CELLS, INCREASES ANGIOGENESIS BUT REDUCES CD8 T-CELL INFILTRATION
IL-24	MELANOCYTES, KERATINOCYTES ,MONOCYTES, T CELLS		PLAYS IMPORTANT ROLES IN TUMOR SUPPRESSION, WOUND HEALING AND PSORIASIS BY INFLUENCING CELL SURVIVAL, INFLAMMATORY CYTOKINE EXPRESSION.
IL-25	T CELLS, MAST CELLS, EOSINOPHILS,MACROPHAGES, MUCOSAL EPITHELIAL CELLS		INDUCES THE PRODUCTION IL-4, IL-5 AND IL-13, WHICH STIMULATE EOSINOPHIL EXPANSION

IL-26	T CELLS, MONOCYTES	ENHANCES SECRETION OF IL-10 AND IL-8 AND CELL SURFACE EXPRESSION OF CD54 ON EPITHELIAL CELLS
IL-27	MACROPHAGES, DENDRITIC CELLS	REGULATES THE ACTIVITY OF B LYMPHOCYTE AND T LYMPHOCYTES
IL-28	-	PLAYS A ROLE IN IMMUNE DEFENCE AGAINST VIRUSES
IL-29	-	PLAYS A ROLE IN HOST DEFENCES AGAINST MICROBES
IL-30	-	FORMS ONE CHAIN OF IL-27
IL-31	TH2 CELLS	MAY PLAY A ROLE IN INFLAMMATION OF THE SKIN
IL-32	-	INDUCES MONOCYTES AND MACROPHAGES TO SECRETE TNF-A, IL-8 ANDCXCL2
IL-33	-	INDUCES HELPER T CELLS TO PRODUCE TYPE 2 CYTOKINE
IL-35	REGULATORY T CELLS	SUPPRESSION OF T HELPER CELL ACTIVATION
IL-36	-	REGULATES DC AND T CELL RESPONSES

EFFECTS:

CYTOKINE	DEFECT	DISEASE
IL-1RA	Under expression	Arthritis
IL-2, IL-7, IL-10, IL-2R, IL-10R	Over expression	IBD (Inflammatory bowel disease)
IL-3	Over expression	Demyelinating Syndrome
IL-10	Under expression	Type-1 Diabetes, Thyroid Disease



DISEASES AND DRUGS USED

DISEASE	DRUG CATEGORY	DRUG	BRAND
Arthritis	NSAIDS, Steroids, Immunosuppressant	Ibuprofen	Motrin
IBD	Anti-inflammatory, Immune System Suppressors, Antibiotics	Sulfasalazine (Azulfidine), prednisone, **Azathioprine, Methotrexate**	Azulfidine, Deltasone, Aprin
Type-1 Diabetes	Peptide hormone	Insulin	Apidra, Humalog, Humulin

PEPTIDE DERIVED AUTACOIDS

- THESE ARE DERIVED FROM PROTEINS
- MADE UP OF LONG CHAINS OF POLYPEPTIDES
- MOST IMPORTANT IN THIS CLASS: ANGIOTENSIN, BRADYKININ

ANGIOTENSIN

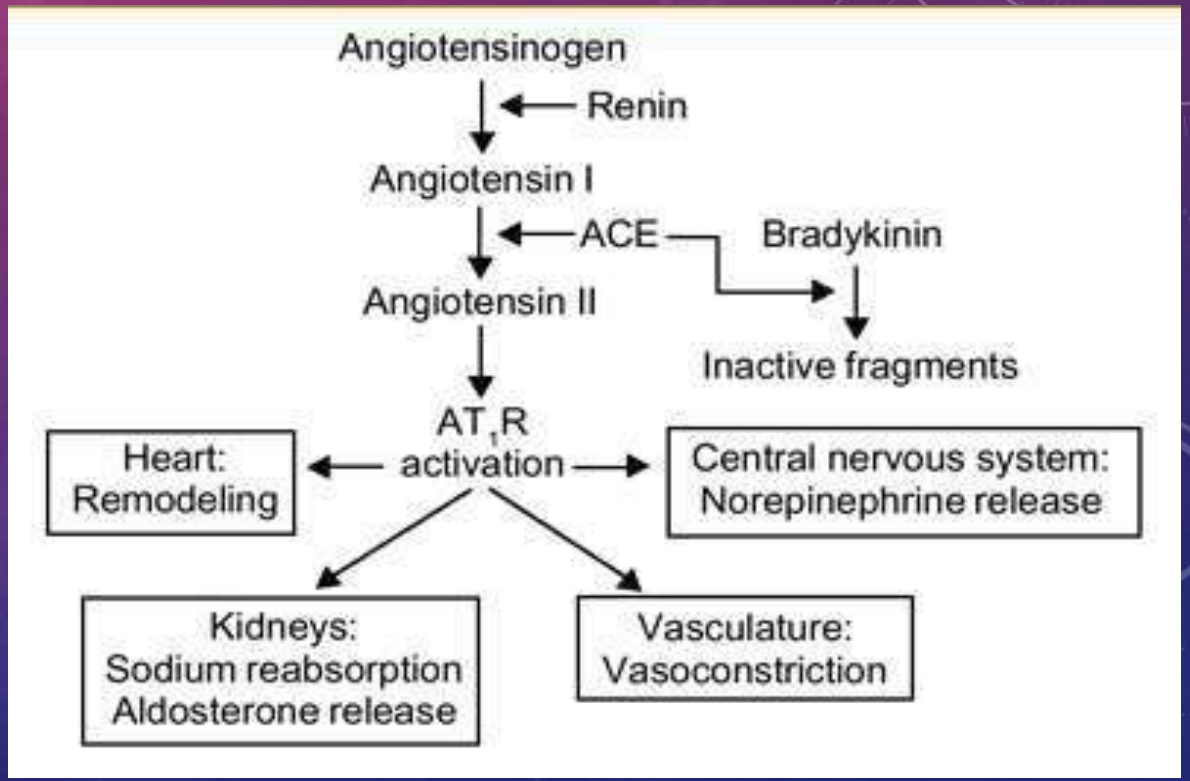
VASOACTIVE PEPTIDE

RENIN-ANGIOTENSIN SYSTEM

REGULATION OF BLOOD PRESSURE

BIOSYNTHESIS OF ANGIOTENSIN

- Renin released from kidney
- Convert angiotensinogen to angiotesin1
- ACE converts angiotensin 1 to angiotensin 2
- Angiotensin 2 exerts action by bindinding to a specific receptor
- Angiotensin 2 degraded by peptidases present in body



COMPONENTS OF RENIN-ANGIOTENSIN SYSTEM

RENIN

- Renin attacks alpha 2 globulin angiotensinogen.
- Renin is glycoprotein and stored in juxtaglomerular cells.
- Secretion of renin from kidney is prime determinant of this system.

Renin secretion is controlled by following factors-

- The mascula densa pathway
- Intrarenal baroreceptor pathway
- Sympathetic nervous system
- Feedback control
- Drugs

COMPONENTS OF RENIN-ANGIOTENSIN SYSTEM

ANGIOTENSINOGEN

- Globular glycoprotein that acts as substrate of renin.
- Synthesized primarily in liver.
- Secretion may be enhanced by inflammation, insulin, estrogens, glucocorticoids, thyroid hormone and angiotensin II.

ANGIOTENSIN CONVERTING ENZYME (ACE)

- Present on the luminal surface of vascular endothelial cells.
- Most important substrates are angiotensin I which it converts into angiotensin substrates which is angiotensin I which it converts into angiotensin II.

ANGIOTENSIN RECEPTORS

- Angiotensin II exerts its actions through specific G protein coupled receptors.
- Two sub types AT_1 and AT_2.
- Most of known action of angiotensin II are mediated through AT_1 receptors.
- Present on vascular smooth muscle, kidney, heart, adrenal gland.
- Most of the actions of angiotensin II such as vasoconstriction, aldosterone release are mediated by AT_1 receptors.
- AT_2 receptors found in adrenal medulla, reproductive tissues, vascular endothelium and parts of the brain
- AT_2 receptors activation causes vasodilation and may exert antiproliferative effects.
- AT_2 receptors may also be involved in foetal tissue development.

FUNCTIONS OF ANGIOTENSIN

CARDIOVASCULAR SYSTEM

- Angiotensin II promotes vasoconstriction
- Directly or indirectly by enhancing Adrenaline/NA release from adrenal medulla/adrenergic nerve endings and by increasing central sympathetic outflow
- Acts as a pressor agent much more potent then NA
- Angiotensin-II increases force of myocardial contraction by promoting Ca^{2+} influx

SMOOTH MUSCLES

- Angiotensin-II contracts many visceral smooth muscles in vitro, but in vivo effects are insignificant

FUNCTIONS OF ANGIOTENSIN

KIDNEY

- Angiotensin II promotes Na^+/H^+ exchange in proximal tube.
- 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

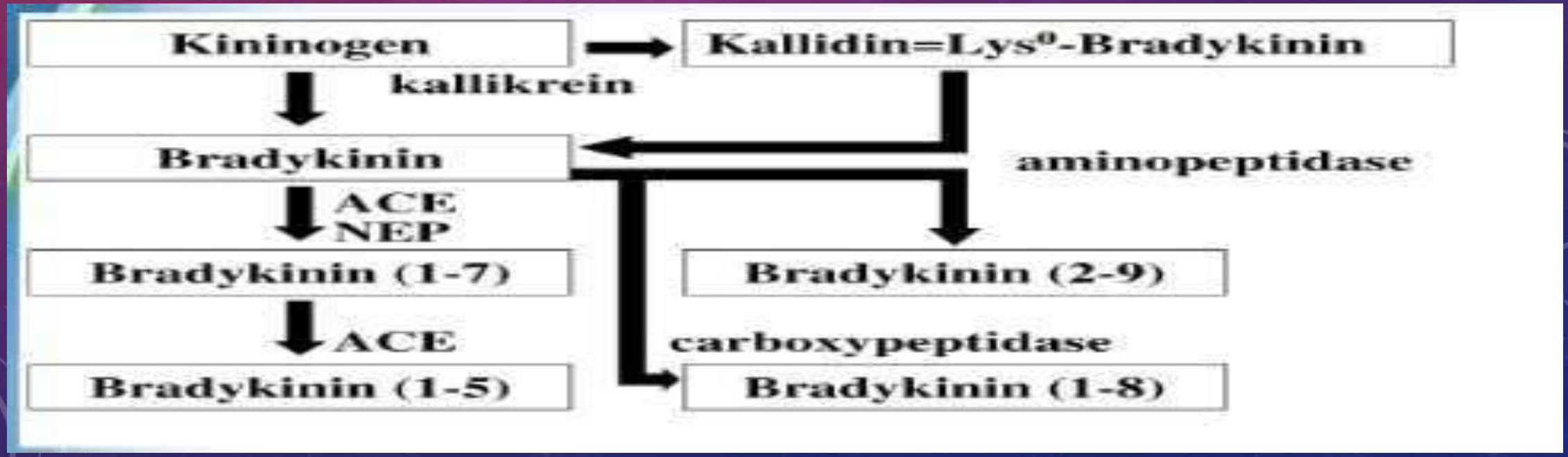
- THE RENIN ANGIOTENSIN SYSTEM PLAYS AN IMPORTANT ROLE IN MAINTAINENCE OF FLUID-ELECTROLYTE BALANCE AND BLOOD PRESSURE
- ANY ABNORMALITY IN THE SYSTEM LEADS TO IMBALANCE IN FLUID LEVELS OF THE BODY LEADING TO RENOVASCULAR HYPERTENSION
- REGULATION OF THE RAAS SYSTEM, THEREFORE BECOMES CLINICALLY IMPORTANT IN THE MANAGEMENT OF HYPERTENSION AND SOME KIDNEY DISORDERS.

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM INHIBITORS

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

BRADYKININS

- Bradykinin formed by proteolytic cleavage of circulating proteins termed kininogens.
- Synthesis and metabolism of Bradykinin



KININS
RECEPTORS, ACTIONS & THERAPY

- Activate β_1, β_2, β_3 receptors linked to PLC/A_2
- Powerful Vasodilation→ decreased blood pressure via β_2 receptor stimulation (NO dependent)
- Increase in capillary permeability inducing edema.
- Produces inflammation & analgesia (β_2)
- Cardiac stimulation:
  - Compensatory indirect & direct tachycardia & increase in cardiac output
  - It produces coronary vasodilation
- Bradykinin has a cardiac anti-ischemic effect, inhibited by β_2 antagonists (NO & PI2 dependent)

PHARMACOLOGICAL ACTIONS

- Vasodilatation
- Increased vascular permeability
- Stimulation of pain nerve endings
- Stimulation of epithelial ion transport and fluid secretion in airways and gastrointestinal tract
- Contraction of intestinal and uterine smooth muscle.

KININS
ACTIONS & THERAPY

- Kinins produce broncho-constriction & itching in respiratory system
- Therapeutic Use:
  - No current use of kinin analogues
  - Increased Bradykinin is possibly involved in the therapeutic efficiency & cough produced by ACEIs