Eicosanoids & Platelet Activating Factor

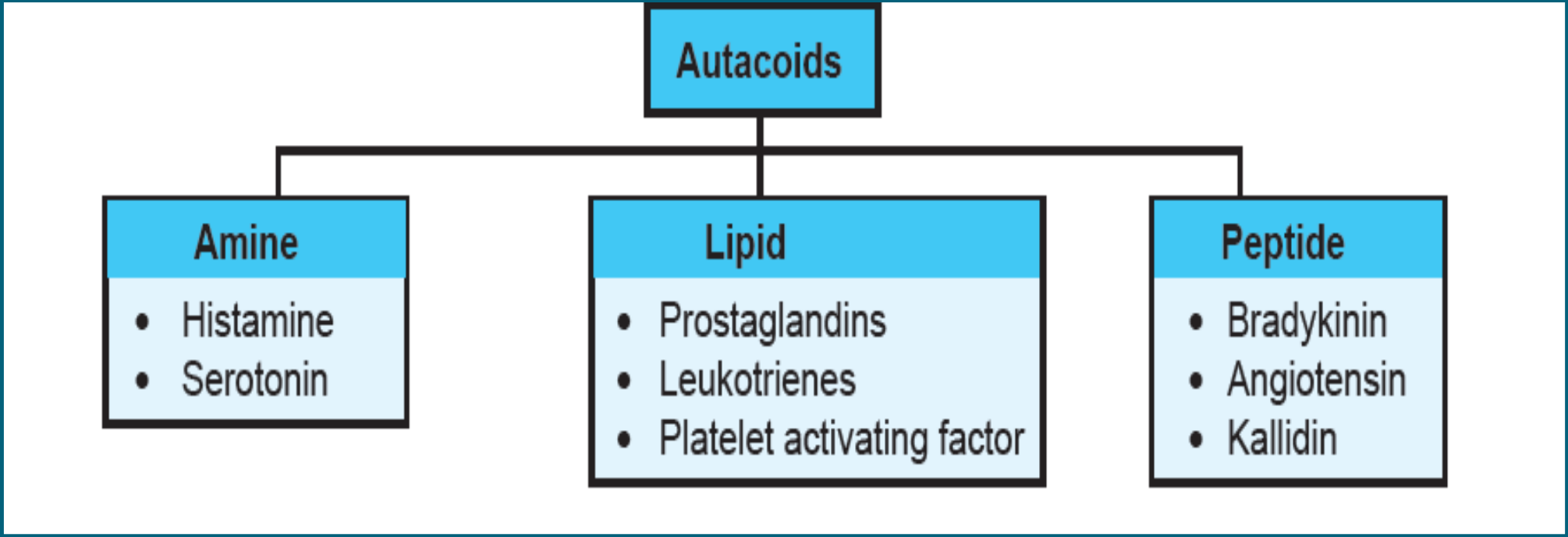
Prof. Sanjay Khattri

Dept. of Pharmacology & Therapeutics

King George's Medical University, Lucknow

Autacoid

- These are the substances produced by wide variety of cells that act locally at the site of production. (local hormones)



Mediators of Inflammation and Immune reaction

1. Vasoactive amines (Histamine and Serotonin)
2. Eicosanoids
3. Platlet Activating Factor
4. Bradykinins
4. Nitric Oxide
5. Neuropeptides
6. Cytokinines

EICOSANOIDS

- PGs, TXs and LTs are all derived from eicosa (referring to 20 C atoms) tri/tetra/ penta enoic acids. Therefore, they can be collectively called *eicosanoids.*
- *Major source: 5,8,11,14 eicosa tetraenoic acid (arachidonic acid).*
- Other eicosanoids of increasing interest are: lipoxins and resolvins.
- The term prostanoid encompasses both prostaglandins and thromboxanes.

EICOSANOIDS Contd….

- In most instances, the initial and rate-limiting step in eicosanoid synthesis is the liberation of intracellular arachidonate, usually in a one-step process catalyzed by the enzyme phospholipase A_2 (PLA_2).

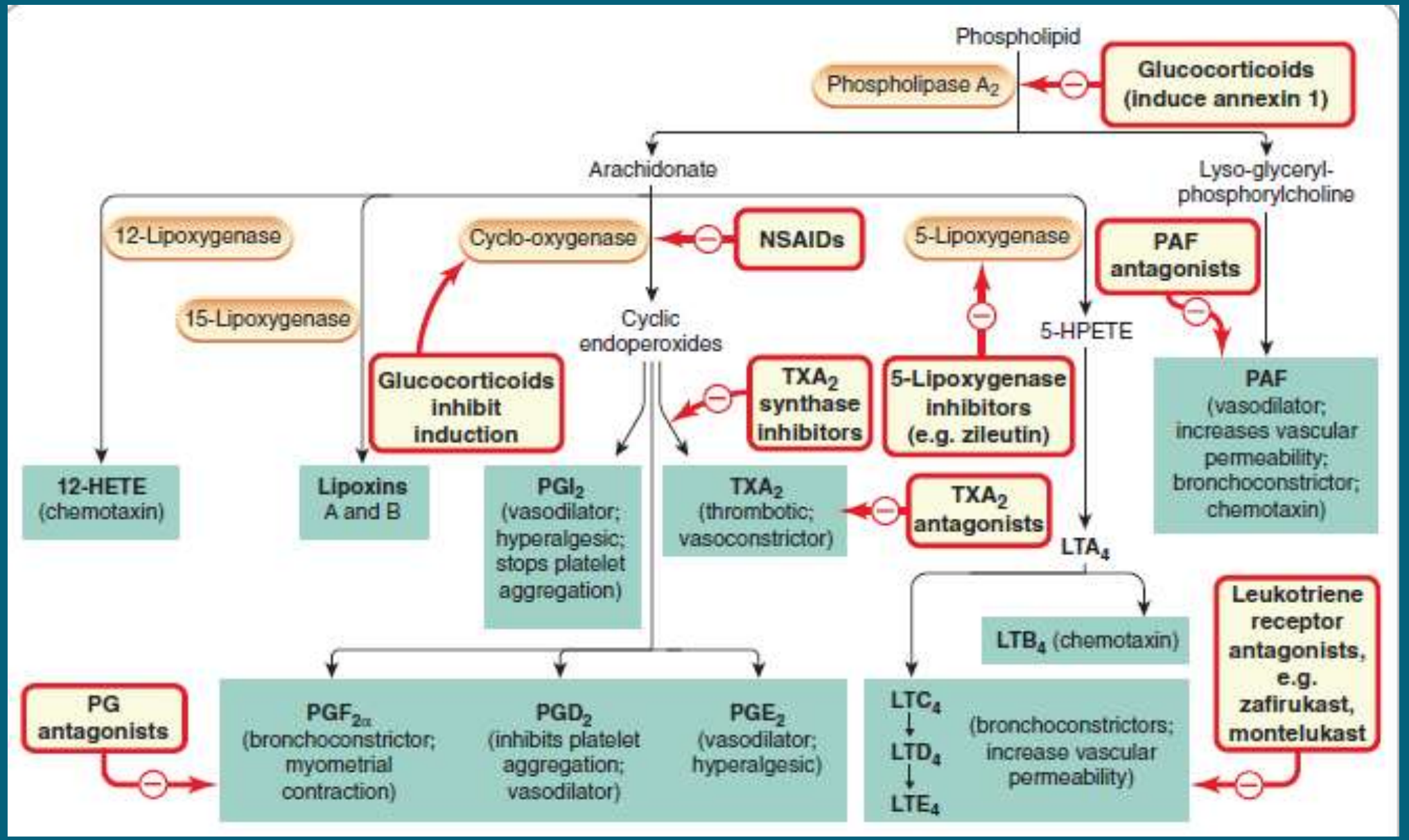
- PLA_2 generates not only arachidonic acid but also lysoglyceryl - phosphorylcholine (lyso-PAF), the precursor of platelet activating factor (PAF).

EICOSANOIDS Contd….

Corticosteroids inhibit the enzyme PLA_2 by inducing the production of lipocortins (annexins).

The free arachidonic acid is metabolised separately (or sometimes jointly) by several pathways, including the following:

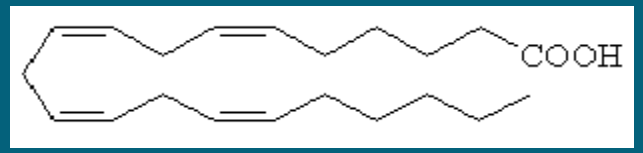
- **Cyclo-oxygenase (COX)**- Two main isoforms exist, COX-1 and COX-2
- **Lipoxygenases-** Several subtypes, which often work sequentially, synthesise leukotrienes.



Summary diagram of the inflammatory mediators derived from phospholipids, with an outline of their actions and the sites of action of anti-inflammatory drugs.

Cell Membrane Phospholipids

Phospholipase A_2



Arachidonic Acid

Cyclooxygenase I&II

Prostaglandin H_2

TXA_2 synthase

PGI_2 synthase

Thromboxane A_2

Prostacyclin (PGI_2)

isomerase

reductase

Prostaglandin D_2

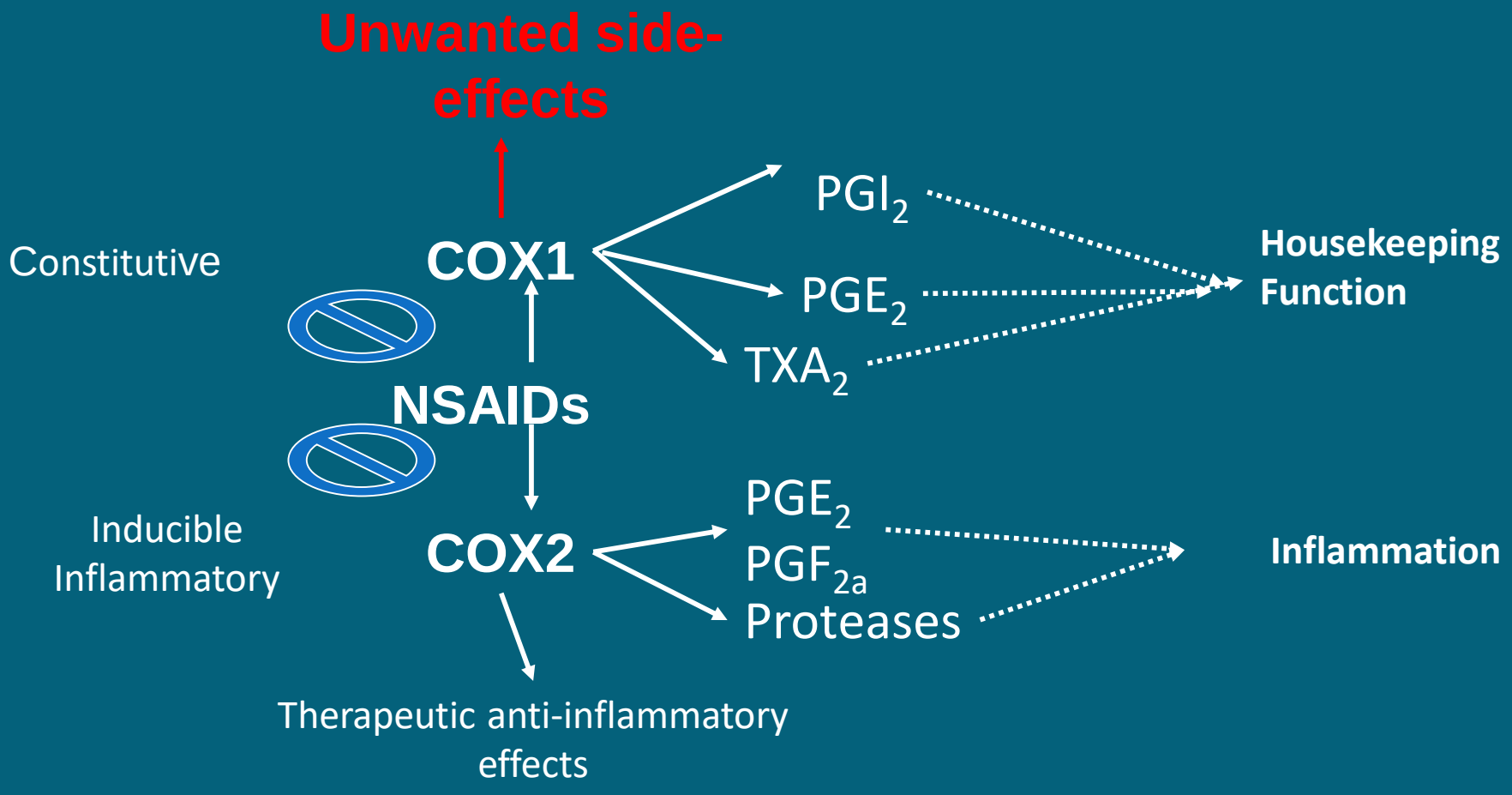
Prostaglandin $F_{2\alpha}$

Prostaglandin E_2

CYCLOOXYGENASES

COX-1	COX-2	COX-3
•Constitutive (always present in cells) •Serves house-keeping function e.g. gastroprotective	•Inducible (synthesis stimulated by endotoxins and other inflammatory mediators) •Participates in inflammation •Constitutive in brain, endothelium and kidney •Procarcinogenic	•Recently isolated from cerebral cortex •Involved in pain perception and fever •Not involved in inflammation •Paracetamol targets COX-3

Differential Actions of Cyclooxygenases



Pathophysiological Roles

CNS

- PGE_1 and PGE_2 are pyrogenic and cause fever.
- NSAIDs act as antipyretic agents by inhibiting these PGs.

Peripheral Nerve Endings

- PGE_2 and PGI_2 sensitize pain receptors to various mediators.
- NSAIDs act as analgesics by decreasing the synthesis of PGs.

Pathophysiological Roles

CVS

- PGE_2, PGI_2 are vasodilators whereas and TXA_2 are vasoconstrictor agents.
- PGI_2 is used in **pulmonary hypertension**
- PGE_2 increases capillary permeability.
- PGE_2 and PGI_2 keeps ductus arteriosus patent.

PLATELETS

- PGI_2 inhibits platelet aggregation whereas TXA_2 is a potent aggregrator of platelets.
- PGI_2 can be used as an anti-aggregratory drug in dialysis and cardiopulmonary bypass, storage of platelets for transfusion.

Pathophysiological Roles

PLATELETS Contd…

- Thromboxane A_2 stimulates blood platelet aggregation, essential to the role of platelets in blood clotting.

UTERUS

- PGE_2 and $PGF_{2\alpha}$ are powerful uterine stimulants (contraction) and cervical ripening
- PGs are responsible for pain during menstruation and NSAIDs like mefenamic acid are useful for relieving this pain.

Pathophysiological Roles

BRONCHUS

- PGE_2 and PGI_2 are bronchodilators and $PGF_{2\alpha}$ & TXA_2 are bronchoconstrictor agents.
- Aerosolized PGE_2 has been used effectively to abort acute attacks of asthma.
- COX inhibitors like aspirin causes more production of LTs.
- Aspirin can result in participation of asthma attacks because LTs are the main bronchoconstricting mediators in human asthma.

Pathophysiological Roles

GIT

- PGE_2 and PGI_2 decreases acid secretion and increases mucus production and mucosal blood flow.
- All these factors decrease the chances of peptic ulcer.
- PGE_2 , $PGF_{2\alpha}$: Spasmogenic, ↑ fluid & electrolyte secretion.

KIDNEY

- PGE_2 and PGI_2 causes renal vasodilation, natriuresis and increased water clearance due to inhibition of the action of ADH. These agents also facilitate renin release.

EYE

- $PGF_{2\alpha}$ decreases intraoccular pressure by increasing the uveoscleral outflow.

Clinical Uses

CVS:

- *Epoprostenol (PGI2) and treprostinil (longer acting PGI2 analogue) can be used for the treatment of pulmonary hypertension.*
- **To keep ductus arteriosus patent** before surgery : *alprostadil* (PGE1) *and epoprostenol* (PGI2)
- **Patent Ductus Arteriosus (PDA)** at birth, *NSAIDs* like aspirin and indomethacin are given to close it.

Platelets:

- *Low dose aspirin* can be used as an *antiplatelet* drug for the prophylaxis of MI and stroke.
- *Epoprostenol* (PGI2) can be used as an *anti-aggregatory drug in dialysis and cardiopulmonary bypass*. It can also be used for storage of platelets for transfusion.

UTERUS:

- Dinoprostone (PGE_2) intravaginally and carboprost (*15-methyl* $PGF_2\alpha$) intraamniotic injection can be used for inducing mid trimester abortion.
- Misoprostol (PGE_1) along with methotrexate or mifepristone is used for induction of abortion in first few weeks of pregnancy.
- *Dinoprostone or misoprostol* intravaginally are employed for *cervical ripening during labour*.
- *Carboprost (15-methyl* $PGF_2\alpha$) can be used to *control post partum hemorrhage* (contraction of uterus leads to compression of blood vessels resulting in decreased bleeding).

Bronchus:

- *Aerosolized PGE2* has been used effectively *to abort acute attacks of asthma.*

- COX inhibitors like aspirin cause more production of LTs (because due to enzyme inhibition arachidonic acid now produces only LTs).

- *Aspirin can result in precipitation of asthma attacks*

GIT

- NSAIDs on long term use can precipitate PUD due to inhibition of PG synthesis.
- *Misoprostol is the most specific drug for the treatment of peptic ulcer due to chronic NSAID use.* [The drug of choice is proton pump inhibitors]
- PG seems to play some role in colonic cancer. *Regular use of aspirin or celecoxib decreases the risk of colonic polyps and cancers.*

KIDNEY

- Loop diuretics act partly by increasing the stimulation of COX; therefore *NSAIDs attenuate the diuretic action* of these drugs.
- **Bartter syndrome** is characterized by *excess PGs* leading to *hyperreninemia, excess aldosterone and the resultant hypokalemia and alkalosis*.
- **Indomethacin** is used for *treatment* of this syndrome.

Male reproductive system

- PGE2 and PGI2 increases sperm motility and enhances penile erection.
- *Alprostadil can be used to treat erectile dysfunction.*

EYE

- PGF2α decreases intraocular pressure **by increasing the uveoscleral outflow.**
- Latanoprost (PGF2α) is being used as eye drops for glaucoma.
- *Bimatoprost, travaprost and unoprostone are new prostaglandin analogues for this indication.*

1. *PGI_2 analogue- Epoprostenol and Treprostinil*

2. *PGE_1 analogue- alprostadil,* Misoprostol

3. *PGE_2 analogue-* Dinoprostone

4. PGF2α analogue- Carboprost

Latanoprost, *Bimatoprost, travaprost and unoprostone*

LEUKOTRIENES

- Leukotrienes are synthesised from arachidonic acid by lipoxygenase-catalysed pathways.
- These soluble cytosolic enzymes are mainly found in lung, platelets, mast cells and white blood cells. The main enzyme in this group is 5-lipoxygenase.
- The 5-lipoxygenase forms 5-hydroperoxytetraenoic acid (5-HPETE), leading to the production of the unstable leukotriene (LT)A_4.
- This may be converted enzymatically to LTB_4 and utilising a separate pathway to the cysteinyl leukotrienes LTC_4, LTD_4, LTE_4.

Leukotrienes cont….

- **LTB4**, acting on specific receptors, causes adherence, chemotaxis and activation of polymorphs and monocytes, and stimulates proliferation and cytokine production from macrophages and lymphocytes.

- LTB4 is an important mediator in all types of inflammation; the cysteinyl leukotrienes are of particular importance in asthma.

- The **cysteinyl leukotrienes** cause: – contraction of bronchial muscle – vasodilatation in most vessels, but coronary vasoconstriction.

Leukotrienes contd….

- **Leukotrienes** have roles in **inflammation**.
- They are produced in areas of inflammation in blood vessel walls as part of the pathology of **atherosclerosis**.
- Leukotrienes are also implicated in **asthmatic** constriction of the bronchioles.

Action of LT s can be inhibited by:

- *Corticosteroids* (decrease the production of LTs by inhibiting phospholipase A2)
- Lipoxygenase inhibitors (*zileuton*)
- LT receptor antagonists (*zafirlukast, montelukast, iralukast*)

PLATELET-ACTIVATING FACTOR

- Platelet-activating factor is a biologically active lipid that can produce effects at exceedingly low concentrations (Gq/G_{11}; stimulates cAMP production).
- PAF is believed to be an important mediator in both acute and chronic allergic and inflammatory phenomena.
- PAF is produced by platelets in response to thrombin, and by activated inflammatory cells.
- **Rupatidine** is a combined H_1 and PAF antagonist that is used for treating allergic symptoms
- **Lexipafant** (PAF antagonist) is in clinical trial in the treatment of acute pancreatitis.

LIPOXINS

- Lipoxins are formed by the concerted action of the 5- and the 12- or 15-lipoxygenase enzymes during inflammation.

- Lipoxins act on polymorphonuclear leukocytes, through a distinct G protein-coupled receptor system to oppose the action of pro-inflammatory stimuli, supplying what might be called ‘stop signals’ to inflammation.

- Aspirin (a COX inhibitor) stimulates the synthesis of lipoxins.

THANK YOU