Prostaglandins (PGs), Thromboxanes (TXs) and Leukotrienes (LTs)

- Eicosanoids are oxygenation products of polyunsaturated long-chain (20 Catom) fatty acids.
- There are considered "local hormones" They have specific effects and they are multiple subfamilies of eicosanoids, e.g. Prostaglandins (PGs), Thromboxanes (TXs) and Leukotrienes (LTs).
- The PGs and TXs are collectively identified as Prostanoids.
- Prostaglandins were originally shown to be synthesized in the prostate gland, thromboxanes from platelets (thrombocytes) and leukotrienes from leukocytes, hence the derivation of their names.
- The eicosanoids produce a wide range of biological effects on inflammatory responses, on the intensity and duration of pain and fever, and on reproductive function. They also play important roles in inhibiting gastric acid secretion, regulating blood pressure through vasodilation or constriction, and inhibiting or activating platelet aggregation and thrombosis.

Bio Synthesis

- Eicosanoids are not stored within cells, but are synthesized as required.
- Two main pathways are involved in the biosynthesis of eicosanoids.
- The prostaglandins and thromboxanes are synthesized by the cyclic pathway, the leukotrienes by the linear pathway.
- Eicosanoids biosynthesis steps;

1) 20-carbon atoms fatty acid (arachidonic acid; AA) formation:

- Eicosanoid biosynthesis begins when a cell is activated by mechanical trauma, cytokines, growth factors or other stimuli.
- This triggers release of a phospholipase at the cell membrane.
- The phospholipase catalyzes ester hydrolysis of phospholipid (by phospholipase A2; PLA)
- This frees a 20-carbon fatty acid (arachidonic acid; AA).

2) Prostanoids formation (cyclooxygenase pathway):

- The cyclic pathway is initiated through the action of prostaglandin G/H synthase (also called prostaglandin-endoperoxide synthase).
- This enzyme possesses two activities, cyclooxygenase (COX) and peroxidase.
- There are two forms of COX activity in humans, COX-1 and COX-2.
- COX-1 (prostaglandin synthase-1; PGS-1) is expressed constitutively in gastric mucosa, kidney, platelets, and vascular endothelial cells.
- COX-2 (prostaglandin synthase-2; PGS-2) is inducible and is expressed in macrophages and monocytes in response inflammation.
- Both COX-1 and COX-2 catalyse the 2-step conversion of arachidonic acid to prostanoids, including prostaglandins (PGs), prostacyclin (PGI2) and thromboxane (TXA2)

3) Leukotrienes formation (Leukotriene pathway):

- The linear pathway is initiated through the action of lipoxygenase (LOX) enzymes of which there are three forms, 5-LOX, 12-LOX and 15-LOX.
- The most actively investigated leukotrienes are those produced by the 5-LOX. The leukotrienes are synthesized by several different cell types including white blood cells (leukocytes), mast cells, lung, spleen, brain and heart.
- The enzyme 5-lipoxygenase (5-LOX) uses 5-lipoxygenase activating protein (FLAP) convert arachidonic acid into protein hydroperoxyeicosatetraenoic acid (5-HPETE), which spontaneously reduces to 5-hydroxyeicosatetraenoic acid (5-HETE).

	- The enzyme LTA synthase acts on 5-HPETE to convert it into leukotriene A4 (LTA4), which may be converted into LTB4 by the enzyme leukotriene A4 epoxide hydrolase. - Leukotriene C4 synthase to conjugate glutathione with LTA4 to make LTC4, which is transported outside the cell, where a glutamic acid moiety is removed from it to make LTD4. The leukotriene LTD4 is then cleaved by dipeptidases to make LTE4. The leukotrienes LTC4, LTD4 and LTE4 all contain cysteine and are collectively known as the cysteinyl leukotrienes.
Inhibition Of Eicosanoid Synthesis	- Corticosteroids block all the known pathways of eicosanoid synthesis. - Non-steroidal anti-inflammatory drugs (NSAIDS) e.g. Aspirin, Indomethacin, block both prostaglandin and thromboxane formation by reversibly inhibiting COX activity. - Aspirin is an irreversible non-selective COX inhibitor. - NSAIDS are not selective for COX-1 or COX-2. - Selective COX-2 inhibitors (e.g. Celecoxib), which were developed more recently. - 5-LOX inhibitor (e.g. Zileuton) and selective antagonists of the CysLT1 receptor for leukotrienes (LTC4, LTD4 and LTE4) (Zafirlukast, Montelukast and Pranlukast, are used clinically in mild to moderate asthma.

Eicosanoid Receptors

- Each of the eicosanoids functions via interactions with cell-surface receptors that are members of the G-protein coupled receptor (GPCR) family.
- There are at least ten characterized prostaglandin receptors. Receptors that bind the prostaglandin D family of lipids are called the DP receptors, those that bind E family prostaglandins are called the EP receptors, those that bind F family prostaglandins are called the FP receptors, those that bind prostacyclin (PGI:) are called the IP receptors, and those that bind the thromboxanes are called the TP receptors.
- There are at least four leukotriene receptors. Two receptors have been characterized that bind LTB4 called BLT1 and BLT2 and two receptors that bind the peptidoleukotrienes (cysteinyl leukotrienes) called CysLT1 and CysLT2.

Eicosanoid	Major Site of Synthesis	Major Biological Activities
PGI2 (Prostacyclin)	Heart and vascular endothelial cells	- Inhibit platelet aggregation. - Induce vasodilation. - decrease T-cell proliferation and lymphocyte migration.
PGE1		- Induce vasodilation. - Inhibit platelet aggregation.
PGE2	Kidney, spleen and heart	- Induce vasodilation - Induce platelet aggregation. - Induce uterine contractions. - Maintaining the open passageway of the fetal ductus arteriosus.
PGD2	Mast cells, eosinophils and brain	- It is a major prostaglandin produced by mast cells. - Induce inflammatory response. - Induces vasodilation. - Induce bronchoconstriction. - Involved in androgenetic alopecia, inhibitors of PGD2 being studied to treat male pattern baldness.
PGF2α	Kidney, spleen and heart	- Induce vasoconstriction. - Induce bronchoconstriction. - Induce smooth muscle contraction.
TXA2	**Platelets**	- Induce platelet aggregation. - Induce vasoconstriction. - Induce bronchoconstriction.
LTB4	Monocytes, basophils, eosinophils, mast cells epithelial cells	- Powerful inducer of leukocyte chemotaxis and aggregation, vascular permeability, T-cell proliferation and secretion of INF-γ (Interferon gamma), IL-1 and IL-2 (Interleukin 1 and 2).
LTC4 **LTD4**		- Component of slow-reactive substance of anaphylaxis and (SRS-A). - Induce vasoconstriction. - Induce bronchoconstriction. - Secretion of INF-γ.
LTE4	Mast cells and basophils	

N.B: SRS-A; is a mixture of the leukotrienes LTC4, LTD4 and LTE4. Mast cells secrete it during the anaphylactic reaction, inducing inflammation.

Effects of Eicosanoids	
Blood vessels	- PGF2a is a vasoconstrictor. - TXA2 is a potent vasoconstrictor, and it also has a smooth muscle mitogenic effects. - PGI2 & PGE2. promote vasodilatation by ↑ cAMP and by intracellular Ca^{2}. - PGI2 inhibits proliferation of smooth muscle cells. - PGD, also has a vasodilator effects, is aldominant mediator of flushing induced by niacin (lipid-lowering drug).
GIT	- Most of the PGs and TXs activate gastrointestinal smooth muscle. - PGE2 & PGF2α Longitudinal muscle contraction. - PGF2α (Strong) & PGI2 (weak) Circular muscle contraction. - PGE2 Circular muscle relaxation. - LTs also have powerful contraction effects.
LUNG	- PGI2 & PGE2 Bronchial smooth muscle relaxation. - PGF2α, TXA2 & PGD2 Bronchial smooth muscle contraction. - Cysteinyl LTs (LTC4, LTD4 and LTE4) Bronchial smooth muscle contraction. - Being about 1000 times more potent than histamine. - Stimulate bronchial mucus secretion and cause mucosal edema. - Bronchospasm occur bout 10% of people taking NSAIDS, because of a shift in arachidonic acid from COX to 5-LOX.
Platelet	- Low concentration of PGE2 enhance platelet aggregation. - High concentration of PGE2 inhibit platelet aggregation. - PGF2α & PGD2 inhibit platelet aggregation. - TXA2 Induce platelet aggregation. TXA2 is the major products of COX-1 isoform enzyme. Platelet COX-1-derived TXA2 biosynthesis is increased during platelet activation and aggregation and is irreversibly inhibited by chronic administration of aspirin at low doses.
	- PGs play important roles in maintaining blood pressure & regulating renal function - COX-1-derived products promote salt excretion in the collecting ducts.
Uterine	- PGF2α & TXA2 uterine smooth muscle contraction. - PGF2α together with oxytocin is essential for the onset of parturition.
Male sex organ	- Smooth muscle-relaxing PGs such as PGE1 enhance penile erection by relaxing smooth muscle of the corpora cavernosa.
BRAIN	**Fever:** - PGE2 increases body temperature. - Endogenous pyrogens release interleukin-1 (IL-1), which in turn promotes synthesis and release of PGE2. - PGE2 synthesis is blocked by aspirin and other antipyretic compounds. **Sleep:** - PGD2 induces natural sleep, while PGE2 cause wakefulness. **Neurotransmission:** - PGE2 may inhibits NE release from postganglionic sympathetic nerve ending.

	Inflammation: PGE2 & PGI2 are the predominant prostanoids associated with inflammation, markedly enhance edema formation and leukocyte infiltration by promoting blood flow in the inflamed region.
EYE	**PGE and PGF derivatives lower intraocular pressure (IOP), by increase aqueous humour outflow (the mechanism is unclear).**
Other	**Bone Metabolism:** **- PGs increase bone turnover by stimulating bone resorption and formation** **Cancer:** **- COX-2 derived PGE2 can promote tumour growth by binding its receptors and activating signalling pathways which control cell proliferation, migration, apoptosis, and/or angiogenesis. However, the prolonged use of high dosages of COX-2 selective inhibitors is associated with unacceptable CV side effects.** **- Large studies and clinical trials indicate that long term use of NSAIDS, can decrease the incidence of certain malignancies, including colorectal. oesophageal, breast, lung, and bladder cancers.**

Prostaglandin Analogues

Synthetic prostaglandin analogues are molecules which are manufactured to bind to a PG receptors.

Prostaglandin E1 Analogues

- PGE, effects Vasodilation, inhibition of platelet aggregation, and stimulation of intestinal and uterine smooth muscle.

Alprostadil (Caverject®)

- Alprostadil is a PGE1 analogue.
- Uses: 1) Maintaining a patent ductus arteriosus in newborns (Firstly; see N.B. below):
- In certain types of congenital heart disease, it is important to maintain the potency of the neonate's ductus arteriosus until corrective surgery can be carried out. This can be achieved with Alprostadil.
- Route of administration: because of rapid pulmonary clearance, it must be continuous IV infusion into a large vein.
- Dose: initial rate: 0.05-0.1 mcg/kg/min, may be increased to 0.4 mcg/kg/min, prolonged infusion has been associated with ductal rupture.
2) Impotence (Erectile Dysfunction; ED):
- Dosage form: urethral suppositories and in injectable form.
- Penile suppository inserted into the urethra.
- Injected by syringe directly into the corpus cavernosum of the penis, avoid injection in midline.
- Onset of action: 5 to 10 minutes.
- Duration of action: Injection 1 to 3 hours, supp.--> 30 to 60 minutes.
- Most common side effects: pain at place of injection or pain of urethra (suppository only) and painful erection.
- N.B:
- The ductus arteriosus, is a normal part of a baby's circulatory system before birth that usually closes shortly after birth. If it remains open, it's called a patent ductus arteriosus.

- **Patent ductus arteriosus (PDA); is a persistent opening between two major blood vessels leading from the heart.**
- **Large patent ductus arteriosus left untreated can allow poorly oxygenated blood to flow in the wrong direction, weakening the heart muscle and causing heart failure and other complications.**
- **PGE1 & PGE2 are responsible for keeping the ductus patent, NSAIDS such as indomethacin or ibuprofen (as IV) may been used to help close a PDA.**
- **NSAIDS during pregnancy in third trimester, increase the risk of premature closure of the ductus arteriosus.**

Misoprostol (Cytotec) (Misotac)

- Misoprostol is a PGE1 analogue, with oxytocic properties.
- It is approved for use in the prevention of NSAID-induced gastric ulcers;
    - NSAIDS inhibit prostaglandin synthesis, and a deficiency of prostaglandins within the gastric mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by these agents.
    - It produces uterine contractions and is contraindicated during pregnancy.
- Off-label uses of Misoprostol:
    - Labor induction, abortion, missed miscarriage and postpartum bleeding;
        - Misoprostol effects are dose dependent and include cervical softening and dilation, uterine contractions.
    - Routes of administration; include oral, vaginal, sublingual, buccal, or rectal.
    - In abortions mainly used in combination with Mifepristone (Antiprogestin).

- Dear pharmacists this drug is prescribed only by obstetricians and gynaecologists by a trusted prescription; So don't prescribe this drug by any way because may be used by prostitutes for abortion (illegally).

Prostaglandin E2 Analogues

Dinoprostone (Cervidil)

- **Dinoprostone is a PGE2 analogue, with oxytocic properties.**
- **It administered vaginally (vaginal insert) for labor induction.**
    - **It cause softening the cervix and causing uterine contraction.**

Prostaglandin F2α Analogues

Carboprost (Hemabate)

- Carboprost is a PGF2 analogue, with oxytocic properties.
- It induces contractions and can trigger abortion in early pregnancy. It also reduces postpartum bleeding.
- Used in treatment of postpartum hemorrhage in the presence of uterine atony that has not responded to usual therapy (i.e., IV oxytocin, uterine massage, IM ergot alkaloids).

Latanoprost (Xalatan)	Bimatoprost (Lumigan)
Travoprost (Travatan)	Unoprostone (Rescula)

- Latanoprost , Bimatoprost , Travoprost and Unoprostone are used as ophthalmic solution to control the progression of glaucoma or ocular hypertension by reducing intraocular pressure.
- Latanoprost was the first prostanoid used for glaucoma, the success of Latanoprost has stimulated development of similar prostanoids with ocular hypotensive effects.
- Used once or twice daily.
- Side effects; irreversible brown pigmentation of the iris and eyelashes, drying of the eyes and conjunctivitis.

- Bimatoprost (LATISSE); is used in treatment of hypotrichosis (inadequate or not enough lashes) to grow eyelashes longer, fuller and darker, Only apply once daily at the base of upper lashes. Don't apply to lower lid, significant improvement by 2 months after starting treatment.

Prostacyclin Analogues

Epoprostenol (Flolan)

- Epoprostenol has 2 major effects:
  1) direct vasodilation of pulmonary and systemic arterial vascular beds,
  2) inhibition of platelet aggregation.
- Used in treatment pulmonary arterial Hypertension (PAH).
- Side effects; Flushing, headache, nausea/vomiting, hypotension, bradycardia and anxiety.