EICOSANOIDS

(PROSTAGLANDINS, LEUKOTRIENES) AND PLATELET ACTIVATING FACTOR

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EICOSANOIDS

- Prostaglandins (PGs) and Leukotrienes (LTs) are biologically active derivatives of 20 carbon atom polyunsaturated essential fatty acids that are released from cell membrane phospholipids.
- PGs, TXs and LTs are all derived from eicosa (referring to 20 C atoms) tri/tetra/pentaenoic acids. Therefore, they can be collectively called eicosanoids.
- Major source: 5,8,11,14 eicosa tetraenoic acid (arachidonic acid).
- The term prostanoid encompasses both prostaglandins and thromboxane.

CHEMISTRY, BIOSYNTHESIS AND DEGRADATION

- Chemically, PGs may be considered to be derivatives of prostanoic acid
- Leukotrienes are so named because they were first obtained from leukocytes (leuko) and have 3 conjugated double bonds (triene).
- During PG, TX and prostacyclin synthesis, 2 of the 4 double bonds of arachidonic acid get saturated in the process of cyclization, leaving 2 double bonds in the side chain. Thus, subscript 2 PGs. e.g. PGE2, PGF2 TXA2.
- No cyclization or reduction of double bonds occurs during LT synthesis- the LTs of biological importance are LTB4, LTC4 and LTD4.

CYCLOOXYGENASE (COX) PATHWAYS

COX- It generates eicosanoids with a ring structure (PGs, TXs, prostacyclin) while lipoxygenase (LOX) produces open-chain compounds (LTs).

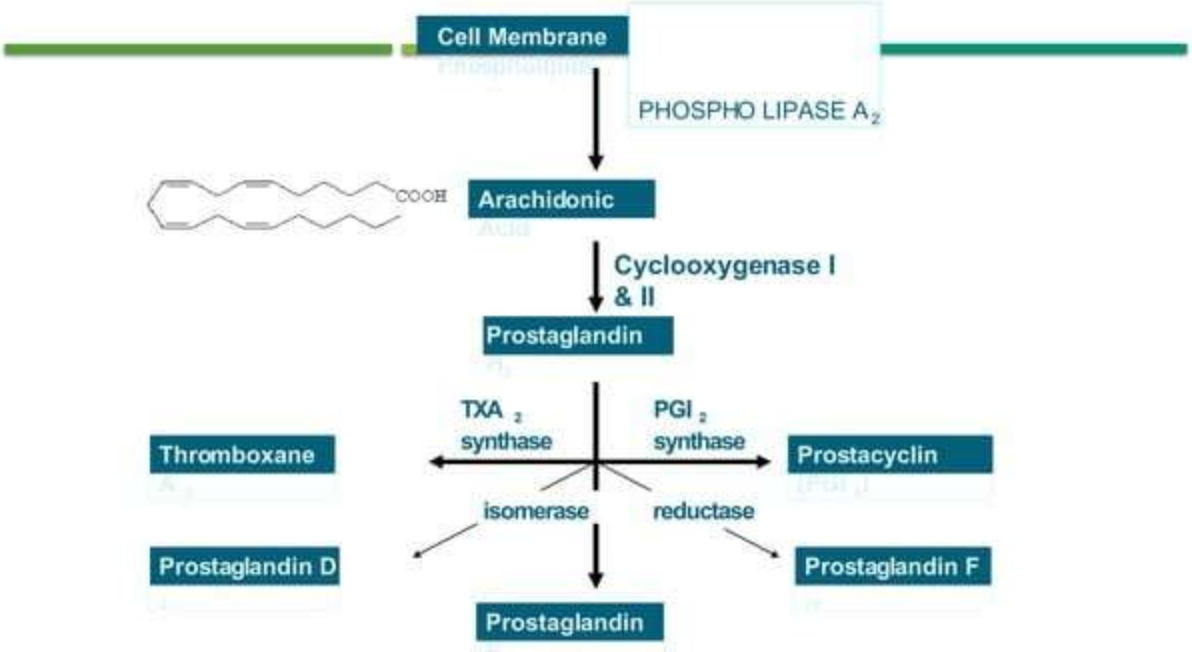
All tissues have COX-can form cyclic endoperoxides PGG2 and PGH2 which are unstable compounds.

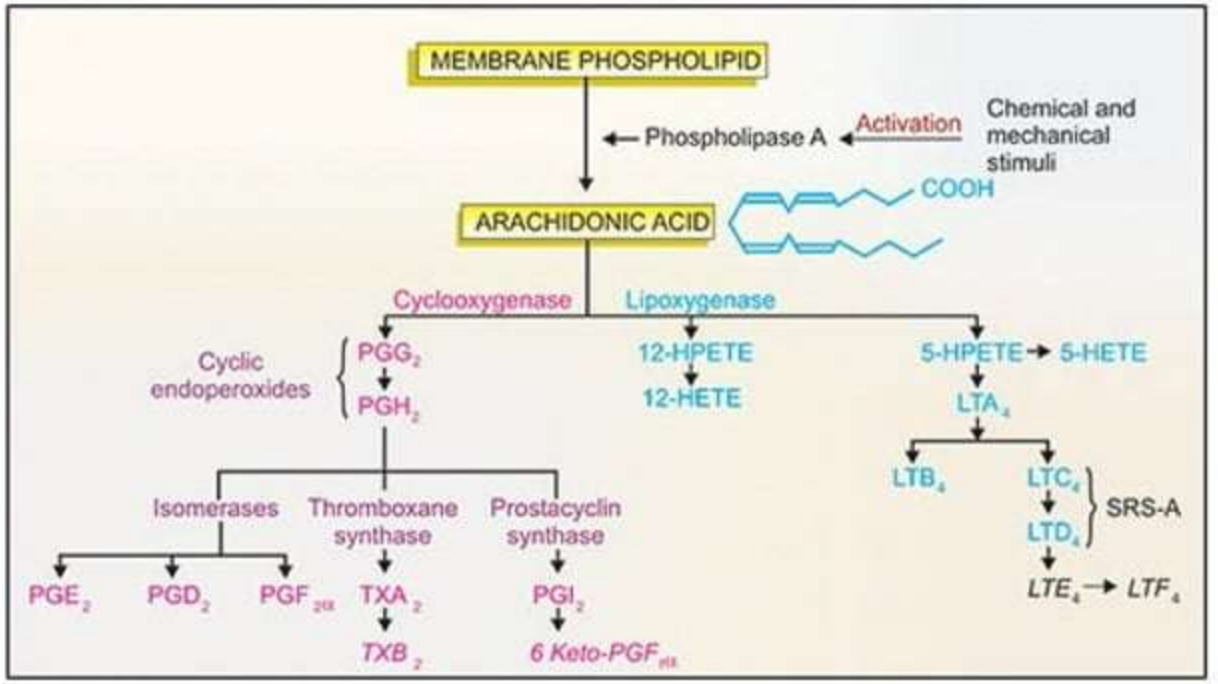
Further course in a particular tissue depends on the type of isomerases or other enzymes present in it. PGE2 and PGF20 are the primary prostaglandins

Platelets primarily synthesize TXA2 which is- chemically unstable, spontaneously changes to TXB2

Endothelium mainly generates prostacyclin (PGI 2).

Cyclo-oxygenase (COX)- Two main isoforms exist, COX-1 and COX-2

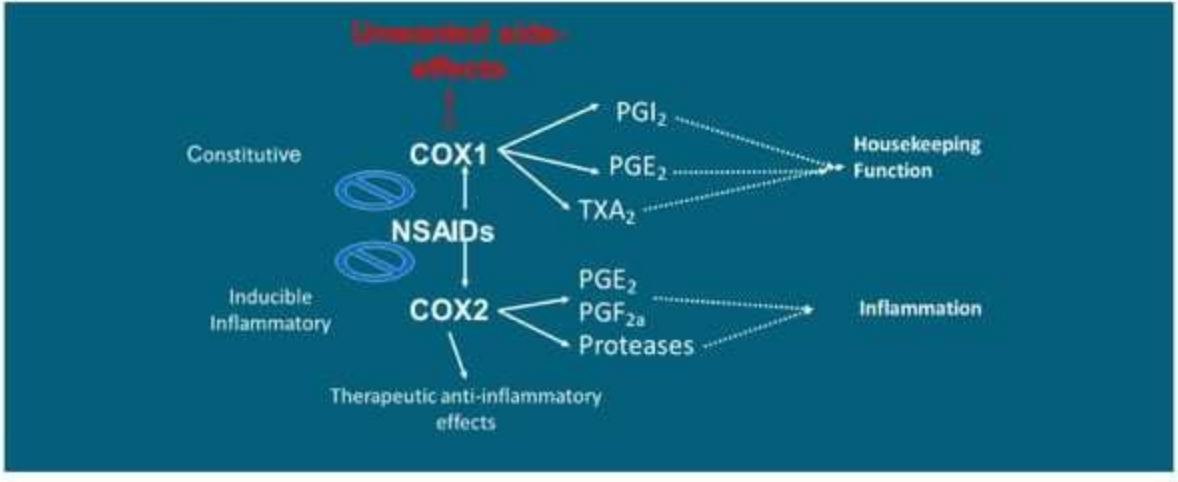

Cell Membrane
PHOSPHO LIPASE A_2
COOH
Arachidonic
Cyclooxygenase I & II
Prostaglandin
TXA_2 synthase
PGI_2 synthase
Thromboxane
Prostacyclin
isomerase
reductase
Prostaglandin D
Prostaglandin F
Prostaglandin


MEMBRANE PHOSPHOLIPID
Phospholipase A
Activation
Chemical and mechanical stimuli
ARACHIDONIC ACID
COOH
Cyclooxygenase
Lipoxygenase
Cyclic endoperoxides
PGG2
PGH2
12-HPETE
12-HETE
5-HPETE
5-HETE
LTA4
LTB4
LTC4
LTD4
SRS-A
LTE4
LTF4
Isomerases
Thromboxane synthase
Prostacyclin synthase
PGE2
PGD2
PGF2α
TXA2
TXB2
PGI2
6 Keto-PGF1α

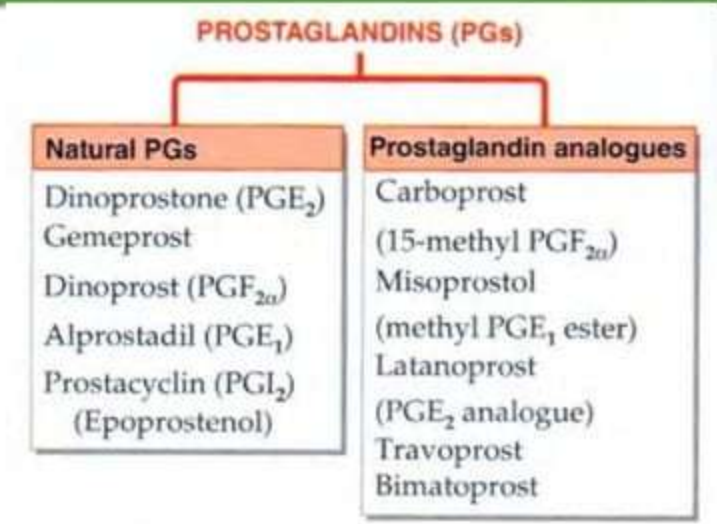
CYCLOOXYGENASES

COX-1	COX-2
•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

ACTIONS OF CYCLOOXYGENASES



CLASSIFICATION OF PROSTAGLANDINS



P. ACTION AND PATHOPHYSIOLOGICAL ROLES

- The cyclic eicosanoids produce a wide variety of actions depending upon the particular PG
- PGs differ in their potency to produce a given action and different PGs sometimes have opposite effects.

PGI_2

- Prostaglandin I_2 receptor (IP_2)
  - GPCR
- cAMP signaling pathway
- PPAR nuclear receptor
- Platelet Inhibition
- Smooth Muscle Relaxation
- Vasodilator

TXA_2

- Thromboxane Receptor (TP)
  - GPCR
- Diacylglycerol (DAG) Inositol 1,4,5-triphosphate signaling pathway (IP3)
  - Increase Ca^{2+}
- Platelet Activation
- Smooth Muscle Contraction
- Vasoconstrictor

P. ACTION AND PATHOPHYSIOLOGICAL ROLES

CVS

- PGE2, PGI2 are vasodilators whereas and TXA2 are vasoconstrictor agents.
- PGI2 is used in pulmonary hypertension
- PGE2 increases capillary permeability.

PLATELETS

- Platelets TXA2, which can be produced locally by platelets, is a potent inducer of aggregation and release reaction.
- On the other hand PGI2 (generated by vascular endothelium) is a potent inhibitor of platelet aggregation.

P. ACTION AND PATHOPHYSIOLOGICAL ROLES

CNS

- PGE1 and PGE2 are pyrogenic and cause fever.
- NSAIDs act as antipyretic agents by inhibiting these PGs.

Peripheral Nerve Endings

- PGE2 and PGI2 sensitize pain receptors to various mediators.
- NSAIDs act as analgesics by decreasing the synthesis of PGs.

UTERUS

- PGE2 and PGF2 a consistently contract human uterus in vivo, both pregnant as well as nonpregnant.
- The sensitivity is higher during pregnancy and there is a progressive modest increase with the advance of pregnancy.

BRONCHIAL MUSCLE

- PGF-2α PGD2 and TXA2 are potent bronchoconstrictors while PGE2 is a powerful bronchodilator. PGl 2 produces mild dilatation.

GIT

- PGE2 and PGI2 decrease acid secretion and increase mucus production.
- PGE2 , PGF2α : Spasmogenic (Peristaltic movement), ↑ fluid & electrolyte secretion.

KIDNEY

- PGE2 and PGI2 cause renal vasodilation, natriuresis and has diuretic effect due to inhibition of the action of ADH. These agents also facilitate renin release.

EYE-

- PGF2u induces ocular inflammation and lowers i.o.t by enhancing uveoscleral and trabecular outflow

Table 13.1 : A summary of the actions of major prostaglandins, prostacyclin and thromboxane

Organ	Prostaglandin E_2 (PGE_2)	Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)	Prostacyclin (PGI_2)	Thromboxane A_2 (TXA_2)
1. Blood vessels	Vasodilatation, ↓ BP	Constricts larger veins and some arteries, 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 (*in vivo*), softening of cervix	Contraction (*in vivo* and *in vitro*), softening of cervix	—	Contraction (*in vitro*)
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, inhibits 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. Afferent nerves	Sensitize to noxious stimuli → tenderness	—	Same as PGE_2	—
11. Endocrine system	Release of ant. pituitary hormones, steroids, insulin; TSH-like action	—	—	
12. Metabolism	Antilipolytic, insulin like action, mobilization of bone Ca^{2+}	—	—	—

T. USES OF PROSTAGLANDINS

1. Abortion

- During the first trimester, termination of pregnancy by transcervical suction is the procedure of choice. intravaginal PGE1 pessary inserted 3 hours before attempting dilatation can minimize trauma to the cervix.
- Medical termination of pregnancy of up to 7 weeks has been achieved with a high success rate by administering mifepristone 600 mg orally 2 days before a single oral dose of misoprostol 400 μg.
- Midterm abortion- a single extra amniotic injection (PGE2) followed by i.v. infusion of oxytocin, or intraamniotic (PGF2) with hypertonic solution

T. USES OF PROSTAGLANDINS

2. Induction/augmentation of labour-

- 1st choice is oxytocin only. PGE2 and PGF2 have been used in place of oxytocin in renal failure patients, because PGs do not cause fluid retention that is possible with oxytocin.
- PGE2 may also be used to augment (speed up) labour if it is slow, intravaginal route is preferred now because side effects are milder.

3. Cervical priming (ripening)-

- Applied intravaginally or in the cervical canal, low doses, of PGE, make the cervix soft and compliant.

T. USES OF PROSTAGLANDINS

4. Postpartum haemorrhage (PPH) Carboprost injected i.m. is an alternative drug for control of PPH due to uterine atony, especially in patients unresponsive to ergometrine and oxytocin.

5. Glaucoma Topical PGF2 analogues like latanoprost, travoprost, bimatoprost are the first choice drugs in wide-angle glaucoma.

6. Peptic ulcer Stable analogue of PGE, (misoprostol) is occasionally used for healing peptic ulcers.

7. To avoid platelet damage PGI2, can be used to prevent platelet aggregation and damage during haemodialysis or cardiopulmonary bypass.

T. USES OF PROSTAGLANDINS

8. Pulmonary hypertension PGI-2 lowers pulmonary artery resistance.

9. Impotence Alprostadil (PGE,) injected into the penis causes an erection lasting 1- 2 hours. However, oral sildenafil is now preferred for erectile dysfunction.

10. To maintain **patency of ductus arteriosus** - PGE (Alprostadil) is used

LEUKOTRIENES

- The straight-chain lipoxygenase products of arachidonic acid are produced by a limited number of tissues (LTB4 mainly by neutrophils; LTC4 and LTD4 - the cysteinyl LTs- mainly by macrophages).
- 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)A4.
- This may be converted enzymatically to LTB4 and then to the cysteinyl leukotrienes LTC4, LTD4, LTE4.

LIPOXYGENASE PATHWAY

- This pathway appears to operate mainly in the lung, WBC and platelets.
- Its most important products are the LTs, (generated by 5-LOX) particularly LTB4 (potent chemotactic) and LTC4, LTD4 which together constitute the 'slow-reacting substance of anaphylaxis' (SRS-A)
- A membrane-associated transfer protein called FLAP (five lipoxygenase activating protein) carries arachidonic acid to 5-LOX and is essential for the synthesis of LTs. Platelets have only 12-LOX.

PHARMACOLOGICAL AND PATHOPHYSIOLOGICAL EFFECTS

- 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.

LT ANTAGONISTS

LTs has no T. Uses.

Action of LT s can be inhibited by:

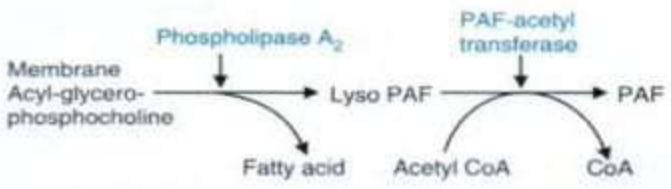
- Corticosteroids (decrease the production of LTs by inhibiting phospholipase A2)
- LT receptor antagonists (zafirlukast, montelukast, iralukast)

PLATELET-ACTIVATING FACTOR

Platelet-activating factor (PAF) is a cell membrane-derived polar lipid with intense biological activity.

Synthesis and degradation

PAF is synthesized from precursor phospholipids present in the cell membrane by the following reactions:



- Antigen-antibody reaction and a variety of mediators stimulate PAF synthesis
- There are no preformed stores of PAF. In contrast to eicosanoids, the types of cells which synthesize PAF is quite limited- mainly WBC, platelets, vascular endothelium and few kidney cells.

ACTIONS

- Platelets PAF induces aggregation and release reaction; also releases TXA_2: i.v. injection of PAF results in intra-vascular thrombosis.
- WBC- PAF is a potent chemotactic for neutrophils, eosinophils and monocytes. It stimulates neutrophils to aggregate, stick to vascular endothelium and migrate across to the site of infection. The chemotactic action may be mediated through release of LTB-4 induces degranulation of eosinophils.
- Blood vessels- Vasodilatation mediated by release of EDRF occurs causing fall in BP on i. v. injection.
- PAF is the most potent agent known to increase vascular permeability. Wheal and flare occur at the site of intradermal injection.

ACTIONS

- Visceral smooth muscle contraction occurs by direct action as well as through release of LTC4, TXA2, and PGs. Aerosolized PAF is a potent bronchoconstrictor. In addition, it produces mucosal edema, secretion and a delayed and long-lasting bronchial hyper-responsiveness. It also stimulates intestinal and uterine smooth muscle.
- In stomach PAF is highly ulcerogenic: erosions and mucosal bleeding occurs shortly afler i.v. injection of PAF. The gastric smooth muscle contracts.

PATHOPHYSIOLOGICAL ROLES

1. Inflammation: Generated by leukocytes at the site of inflammation PAF appears to participate in the causation of vasodilatation, exudation, cellular infiltration and hyperalgesia.

2. Bronchial asthma: PAF appears to play a major role by causing bronchoconstriction, mucosal oedema, recruiting eosinophils and provoking secretions. It is unique in producing prolonged airway hyper-reactivity. (Asthma)

3. Anaphylactic shock conditions: are associated with high circulating PAF levels.

4.Haemostasias and thrombosis: PAF may participate by promoting platelet aggregation.

5. PAF may also play a role in implantation of a fertilized ovum, ischaemic states of brain, heart and g.i.t., including g.i. ulceration.

PAF has no T. Uses.

PAF antagonist

- **Rupatidine** is a combined H1 and PAF antagonist that is used for treating allergic symptoms
- **Lexipafant** (PAF antagonist) is in clinical trial in the treatment of acute pancreatitis.
- **Alprazolam and triazolam** antagonize some actions of PAF.


THANK YOU