Prostaglandins, Thromboxanes and Leukotrienes.

Subject: Pharmacology II
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PROSTAGLANDINS AND LEUKOTRIENES

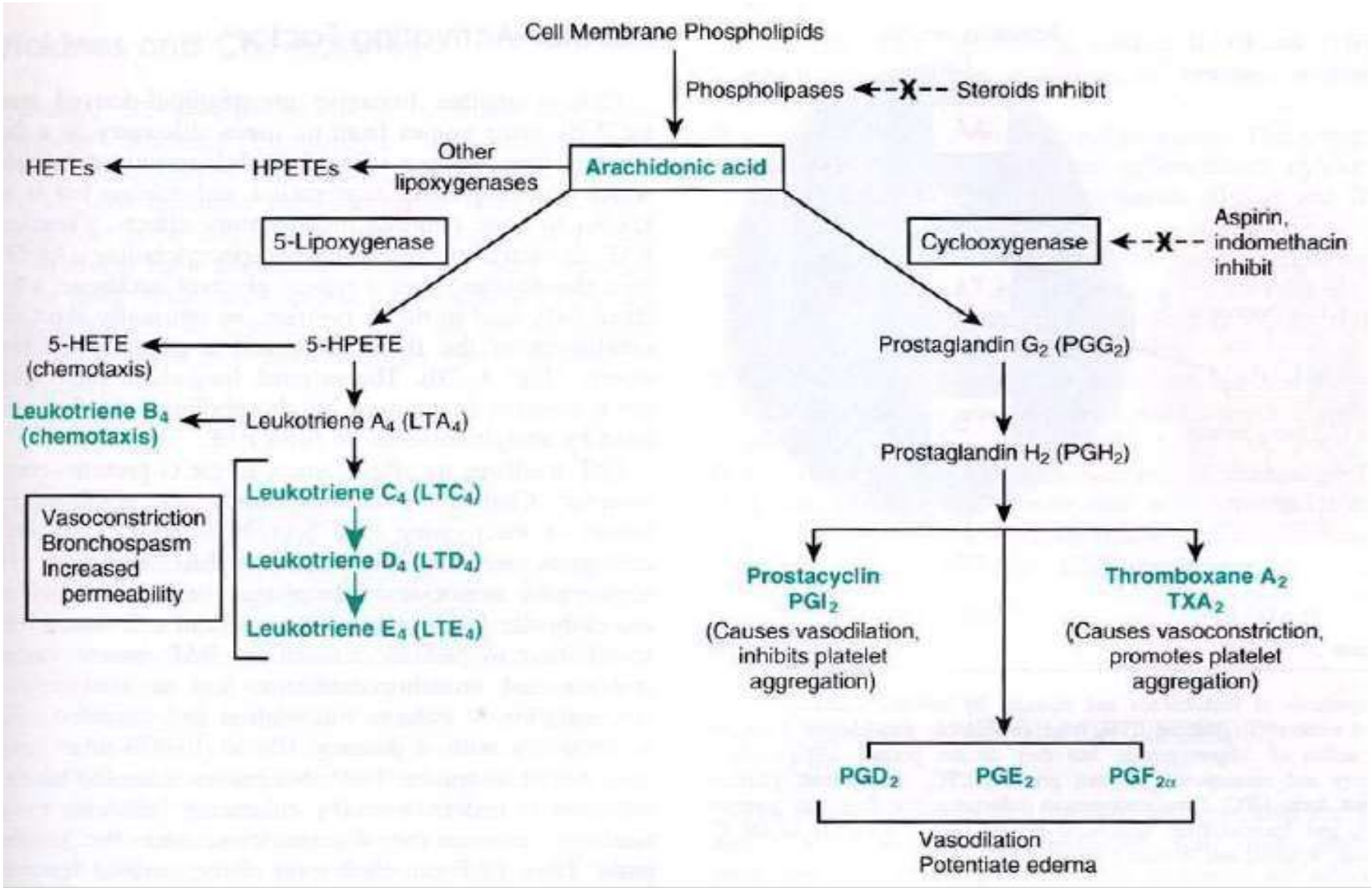
- Prostaglandins (PGs) and Leukotrienes (LTs) are biologically active derivatives of 20 carbon atom polyunsaturated essential fatty acids that are released from cell membrane phospholipids.
- They are the major lipid derived autacoids
- In the body PGs, TXs and LTs are all derived from eicosa (referring to 20 C atoms) tri/tetra/ penta enoic acids. Therefore, they can be collectively called *eicosanoids.*

BIOSYNTHESIS

- In human tissues, the fatty acid released from membrane lipids in largest quantity is *5,8,11,14 eicosa tetraenoic acid (arachidonic acid).*

- *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 are the most important in man, e.g. PGE2, PGF2α, PGI2, TXA2.
- No cyclization or reduction of double bonds occurs during LT synthesis—the LTs of biological importance are LTB4, LTC4, LTD4.

The pathways of biosynthesis of eicosanoids



Cyclooxygenase

- Cyclooxygenase is known to exist in two isoforms COX-1 and COX-2.

- While both isoforms catalyse the same reactions, COX-1 is a constitutive enzyme in most cells—it is synthesized and is active in the basal state; the level of COX-1 activity is not much changed once the cell is fully grown.
- On the other hand, COX-2 normally present in insignificant amounts, is inducible by cytokines, growth factors and other stimuli during the inflammatory response.
- It is believed that eicosanoids produced by COX-1 participate in physiological (house keeping) functions such as secretion of mucus for protection of gastric mucosa, haemostasis and maintenance of renal function,
- while those produced by COX-2 lead to inflammatory and other pathological changes. However, certain sites in kidney, brain and the foetus constitutively express COX-2 which may play physiological role.

Lipoxygenase

- 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.

Inhibition of synthesis

- Synthesis of COX products can be inhibited by nonsteroidal antiinflammatory drugs (NSAIDs).
- *Zileuton inhibits LOX and decreases the production of* LTs.
- Glucocorticosteroids inhibit the release of arachidonic acid from membrane lipids.

Degradation

- Biotransformation of arachidonates occurs rapidly in most tissues, but fastest in the lungs.
- Most PGs, TXA2 and prostacyclin have plasma t½ of a few seconds to a few minutes. First a specific carrier mediated uptake into cells occurs, the side chains are then oxidized and double bonds are reduced in a stepwise manner to yield inactive metabolites.
- Metabolites are excreted in urine. PGI2 is catabolized mainly in the kidney.

ACTIONS AND PATHOPHYSIOLOGICAL ROLES

- **Prostaglandins, thromboxanes and prostacyclin**

1. **CVS:** PGI2 is uniformly vasodilatory and is more potent hypotensive than PGE2.

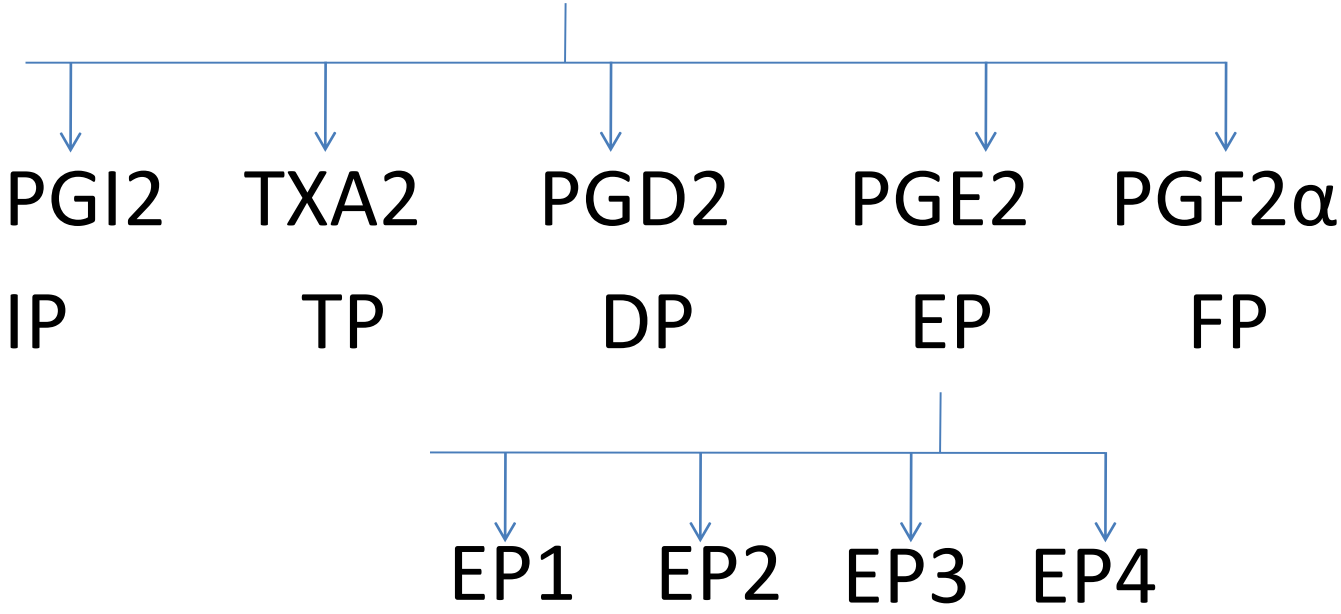
- TXA2 consistently produces vasoconstriction.
- PG endoperoxides (G2 and H2) are inherently vasoconstrictor, but often produce vasodilatation or a biphasic response due to rapid conversion to other PGs, especially PGI2 in the blood vessels themselves.
- PGE2 and F2α stimulate heart by weak direct but more prominent reflex action due to fall in BP. The cardiac output increases.

- **Platelets:**TXA2 produced by platelets inducing aggregation on injury, when plugging and thrombosis are needed.
- **Uterus:**PGE2 and PGF2α uniformly contract human uterus. Used in abortion and can induced labour.
- **Eye:** PGF2α decrease intraoccular tension and used in glucoma.
- **GIT:** PGE2 reduce acid secreation in the stomach. PGI2 also inhibit acid secreation but in less extent. PGE2 and PGI2 increase the secration of gastric mucosa in stomach act as cytoprotective.
- **Kidney:** PGE2 and PGI2 increase water ,sodium and potassium excretion and have diuretic effect.
- **Bronchial muscle**: PGF2α, PGD2 and TXA2 are potent bronchoconstrictor while PGE2 is a powerful bronchodilator.

- Leukotrienes
- **Smooth muscle**: LTC4 and LTD4 are potent bronchoconstrictor and are primary component of slow reacting substance of anaphylaxis i.e secreated in asthma and anaphylasis.
- **Afferent nerve:** LTB2 also sentizes afferent carrying pain impulse contributes to pain and tenderness of inflammation.
- **CVS and blood:** LTC4 and LTD4 injected i.v evoke a brief rise in BP follwed by more prolong fall.

Receptor

- Main class of PG:



- All are G-protein coupled receptors.
- IP3/DAG or CAMP transducer mechanism.

PG	Receptor	Functions
PGD2	DP	Vasodilatation, Relaxation of GIT & uterus, regulates Sleep-wake cycle. Inhibit platelet aggregation.
PGF2	FP	Contractions Uterus & Bronchi.
PGI2	IP	Inhibit platelet aggregation, Vasodilatation
TXA2	TP	P. aggregation, Vasoconstriction, Bronchoconstriction
PGE2	EP 1-3	EP1- Bronchonstrction, GIT motility EP2- Br.dilation, Vasodilatation, GIT relaxation EP3 – inhibit gastric acid secretion, Cytoprotective action

LT receptors

- LTB4 - BLT receptors
- LTC4 /LTD4 /LTE4 - cyst LT receptors.
- LT R are G-protein coupled & function through IP3/DAG transduction mechanism.
- LT inhibitor-
- Zileuton LOX inhibitor- inhibit LT induced responses.
- LT receptor antagonists- Zafirlukast, Montelukast & Iralukast. Antiasthmatic & Anti-inflammatory agent.

Uses of Prostaglandin analogues

1.**Abortion**

- Dinoprostone - PGE2.
  - Induction of mid-term abortion.
  - Cervical ripening & induction of labour at full term.
  - Not used for menstrual regulation/early abortion.
- Carboprost - PGF2α
  - Used for mid-term abortion.
- Misoprostol -PGE1
  - used for abortion

2. **Glaucoma**

Latanoprost (PGF2α) - Reduces I.O.P

3.Ulcer healing-

Misoprostol -PGE1

Ulcer protective agent

Enprostil - PGE2.

Used in NSAID's induced P.U & Chronic smokers.

4. To prevent platelet aggregation-

Epoprostenol- PGI2

Haemodialysis & Cardiopulmonary bypass.

5. Facilitation of labour-

Dinoprostone - PGE2

Vaginally- softens the cervix before labour induction.

Side effect

- Side effects are common in the use of PGs, but their intensity varies with the PG, the dose and the route.
- These are: nausea, vomiting, watery diarrhoea, uterine cramps, unduly forceful uterine contractions, vaginal bleeding, flushing, shivering, fever, malaise, fall in BP, chest pain.