Eicosanoids

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Eicosanoids (eicosa- in Greek: twenty) are special lipid molecules that are derived from arachidonic acid and some other (C_{20}) polyunsaturated fatty acids. They include:

- Prostanoids which are prostaglandins (PG), prostacyclins (PGI) and thromboxanes (TX).
- leukotrienes (LT).

The term "prostaglandins" is often used loosely to include all prostanoids.

Origin of the name : Prostaglandins were first discovered in seminal fluid in 1930s when it was observed that fatty acid-derived molecules in the seminal plasma could cause contraction or relaxation of smooth muscles and were thought to be derived from prostate gland , hence the name prostaglandins. However, they were later discovered in most mammalian tissues.

Prostaglandins have a hormonal like action. They are metabolized into non-active products at their sites of synthesis and are not stored in any tissue. They are, therefore, sometimes called local hormones or autocrine or paracrine hormones. They are extremely potent compounds that elicit a wide range of responses, both physiologic (inflammatory response) and pathologic (hypersensitivity). Prostaglandins ensure gastric integrity and normal renal function, regulate smooth muscle contraction (intestine and uterus are key sites) and blood vessel diameter, and maintain platelet homeostasis. Prostaglandins biologic actions are mediated by plasma membrane G protein–coupled receptors (GPCRs) on the surface of target cells, which are different in different organ systems, and typically result in changes in cAMP production.

Eicosanoid structure and nomenclature:

Prostaglandins are oxygenated C_{20} unsaturated F.As containing a cyclopentane ring. They can be considered to be derivatives of a hypothetical parent compound which is called prostanoic acid. They are divided into groups (A to– J) depending on the *substitutions* on the cyclopentane ring, and further subdivided by being assigned a number corresponding to *the number of double bonds* in the side chains. For example, $PGF_{2\alpha}$ has two –OH substitutions on the ring, has two double bonds, and these substitutions are directed below the plane of the cyclopentane ring (alpha position or isomer).

Thromboxanes were so named because their synthesis was first demonstrated in thrombocytes (platelets) and they contain an oxane ring.

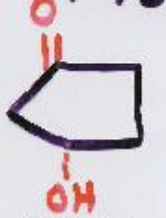
Eicosanoids

eicosa - in Greek: twenty

- Prostanoids
  - Prostaglandins
  - Thromboxanes
  - Prostacyclins
- Leukotriens LT

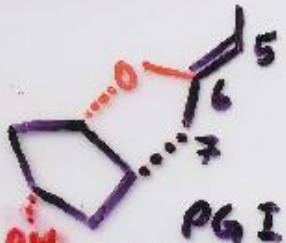
Prostanoic acid

PG G+H



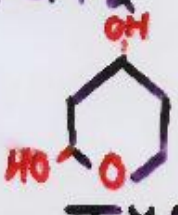
PG E

PG Fα



PG I
(Prostacyclin)

TXA



TXB

Eicosanoids synthesis:

- **Arachidonic acid is oxygenated by:**
  - **The cyclooxygenase (COX)**
  - **Lipoxygenase (LOX)**

Source of arachidonic acid: Arachidonic acid is derived from the C_2 position of phospholipids, as a result of phospholipase A_2 activity.

Inhibitors of eicosanoid synthesis: Phospholipase A_2 is inhibited by corticosteroids which are thus potent anti-inflammatory agents.

Inhibitors of prostaglandin synthesis: Cyclooxygenase itself can be inhibited by aspirin (acetylsalicylic acid) which inhibits the enzyme irreversibly by acetylating a serine residue in its active site, i.e., it is an irreversible inhibition. Ibuprofen and indomethacin (non-steroidal anti-inflammatory drugs, NSAID) on the other hand, are both competitive inhibitors of the cyclooxygenase.

The pathway of prostanoid synthesis:

Prostanoid synthesis involves the consumption of two molecules of oxygen by *prostaglandin endoperoxide synthase* , a microsomal enzyme which possesses two separate enzyme activities, a *cyclooxygenase* and a *peroxidase* activity resulting first in the formation of PGG_2 followed by PGH_2 , both are endoperoxides.

Isomerases can convert PGH_2 into PGD , PGE and PGF while *TX synthase* can converts PGH_2 into thromboxane (TX) and *prostacyclin synthase* converts PGH_2 it into prostacyclin (PGI).

PG degradation: A prostaglandin may be degraded into malondialdehyde (MDA) which is a C_3 molecule plus a C_{17} molecule called hydroxyheptadecatrienoic acid.

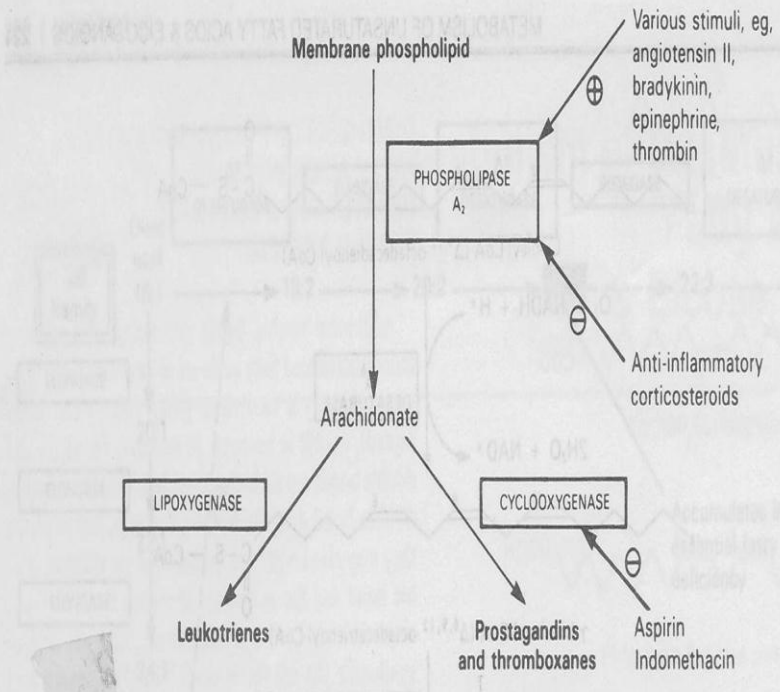
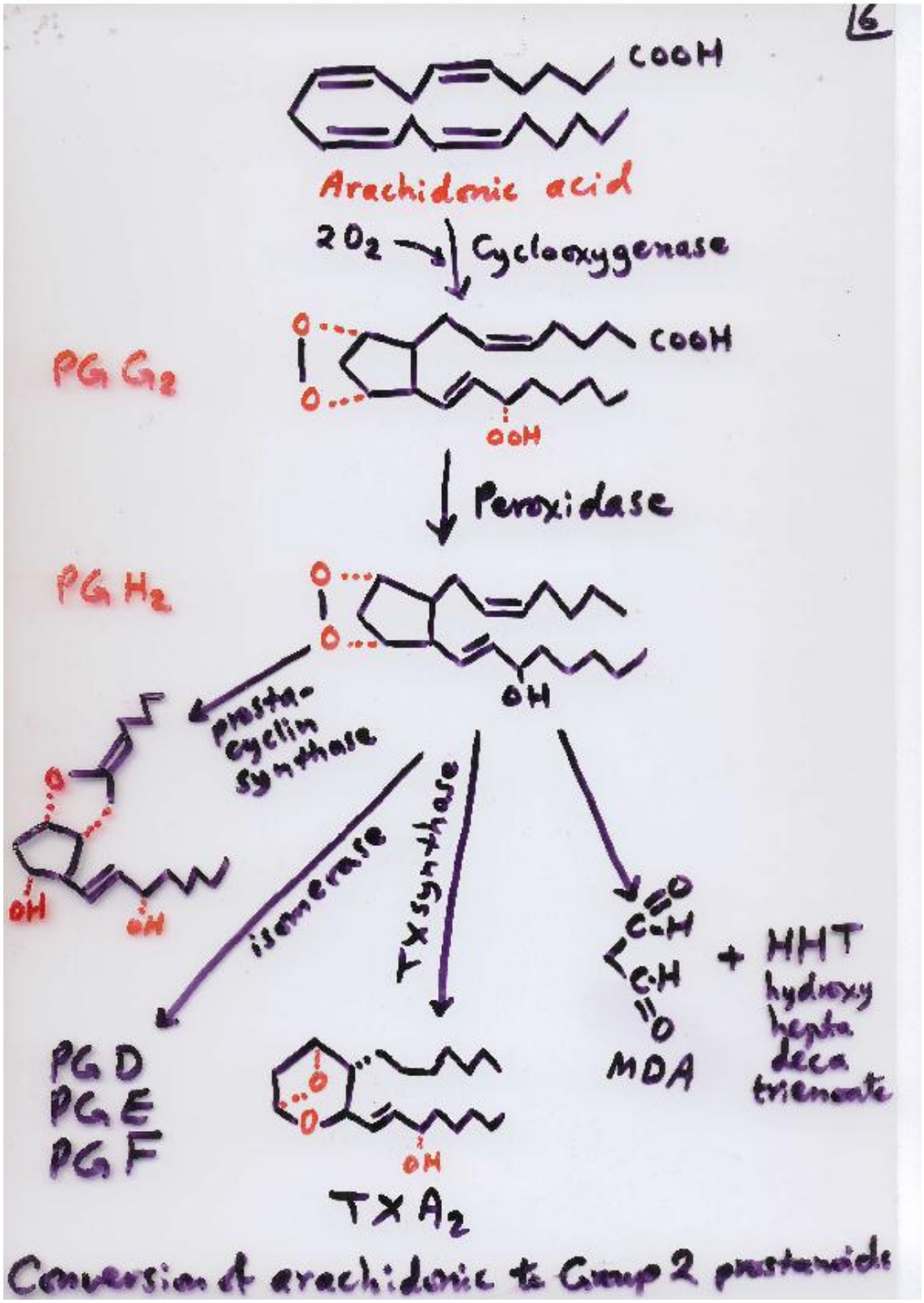


Figure Conversion of arachidonic acid to prostaglandins and thromboxanes via the cyclooxygenase pathway and to leukotrienes via the lipoxygenase pathway. The figure indicates why steroids, which inhibit total eicosanoid production, are better antiinflammatory agents than aspirinlike drugs, which only inhibit the cyclooxygenase pathway. Antiinflammatory steroids are thought to inhibit phospholipase A_2 through induction of an inhibitory protein named lipocortin.


16
COOH
Arachidonic acid
$2O_2$
Cyclooxygenase
PG G_2
COOH
OOH
Peroxidase
PG H_2
OH
prosta-
cyclin
synthase
isomerase
TX synthase
PG D
PG E
PG F
OH
TX A_2
MDA
+ HHT
hydroxy
hepta
deca
trienoate
Conversion of arachidonic to Group 2 prostanoids

Importance of prostaglandins:

PGs are potent biologically active substances. As little as 1 ng / ml of a certain PG can cause contraction of smooth muscles in animals. PGs are involved in a wide variety of conditions.

1. They can increase capillary permeability during inflammatory response and contribute to prolonged erythema, swelling and oedema as well as production of pain.
2. During pregnancy, they are produced in response to oxytocin and promote uterine contraction. Therefore, PGs have been used in termination of pregnancy, in induction of labor, and in prevention of pregnancy. This is by enhancing muscular contraction.
3. In the temperature regulating center of the hypothalamus, the PG synthesis and release is activated by pyrogens leading to production of fever. Aspirin is an antipyretic drug by virtue of its ability to inhibit PG synthesis.
4. PGs inhibit HCl secretion & promote mucus secretion in the stomach and therefore; the inhibition of PG synthesis by some analgesics (NSAIDs; non-steroidal anti-inflammatory drugs) will increase HCl secretion and at the same time inhibits the formation of the protective mucus. This may cause damage to the gastric mucosa.

Role of prostaglandins in platelet homeostasis

TXA_2 is synthesized by COX-1 in activated platelets and upon release causes vasoconstriction and platelet aggregation. PGI_2 is produced by COX-2 in vascular endothelial cells and is a potent inhibitor of platelet aggregation and promotes vasodilatation. Thus TXs and PGIs are antagonistic in action. The opposing effects of TXA2 and PGI2 would limit thrombi formation to the site of vascular injury.

[Note 1: Aspirin has an anti-thrombogenic effect. First: It inhibits TXA_2 synthesis by COX-1 in platelets and PGI_2 synthesis by COX-2 in endothelial cells through irreversible acetylation of these isozymes. Second: The inhibition of COX-1 cannot be overcome in platelets which lack nuclei. However, the inhibition of COX-2 can be overcome in endothelial cells, because they have a nucleus and, therefore, can generate more of the enzyme. This difference is the basis for the use of low-dose aspirin therapy to lower the risk of stroke and heart attacks by decreasing formation of thrombi.]

[Note 2: The low incidence of heart disease in Greenland Eskimo is believed to be due to their intake of fish oils containing eicosapentaenoic acid which gives rise to a potent prostacyclin and a weak thromboxane, thus the balance is shifted towards vasodilatation and non-aggregation of platelets.

Leukotrienes (LK):

These are *conjugated trienes* that are formed from eicosanoic acids in leucocytes, mast cells, platelets and macrophages in response to both immunologic and non-immunologic stimuli.

LK synthesis: Their pathway of synthesis is called the lipooxygenase (LOXs) pathway. For example, 5- lipoxygenase (5-LOX) converts arachidonic acid to 5-hydroperoxy-6, 8,11,14 eicosatetraenoic acid (5-HPETE). 5-HPETE is converted to a series of leukotrienes containing four double bonds, the nature of the final product varies according to the tissue. By 5-LOX action, the first product is LK A_4 which is an epoxide in nature, if hydrolyzed then converted into LK B_4 but if add glutathione then converted into LK C_4, the latter minus glutamic acid then LK D_4, the latter minus glycine then LK E_4 (see the figures).

LK synthesis is not inhibited by NSAIDs. On the contrary, when medications such as NSAIDs or aspirin block the COX-1 enzyme, production of thromboxane and some anti-inflammatory prostaglandins is decreased, and in patients with a condition called Aspirin-induced asthma there is overproduction of pro-inflammatory leukotrienes, which can cause severe exacerbations of asthma and allergy-like symptoms.

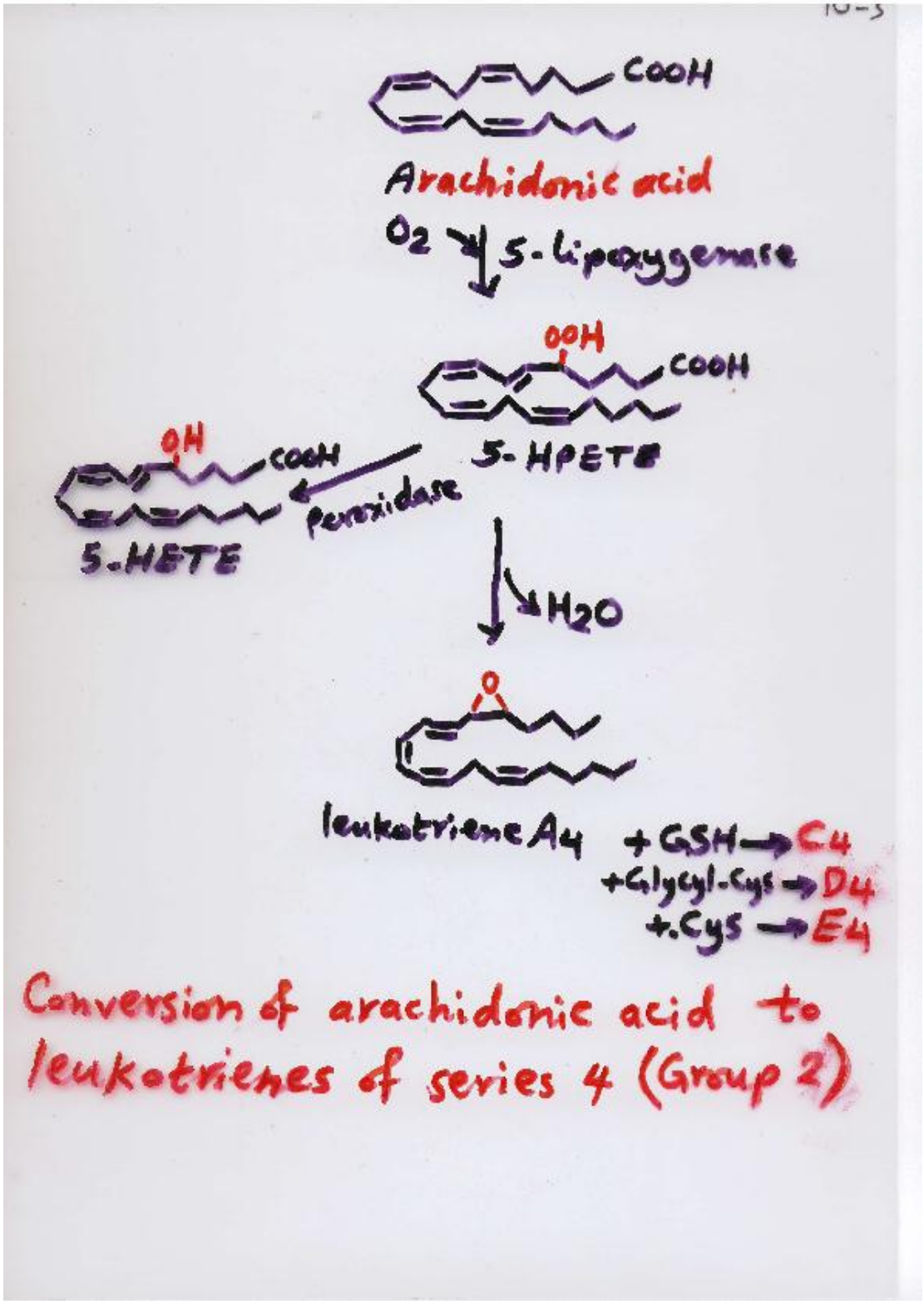
LK synthesis is inhibited by 5-lipoxygenase inhibitors.

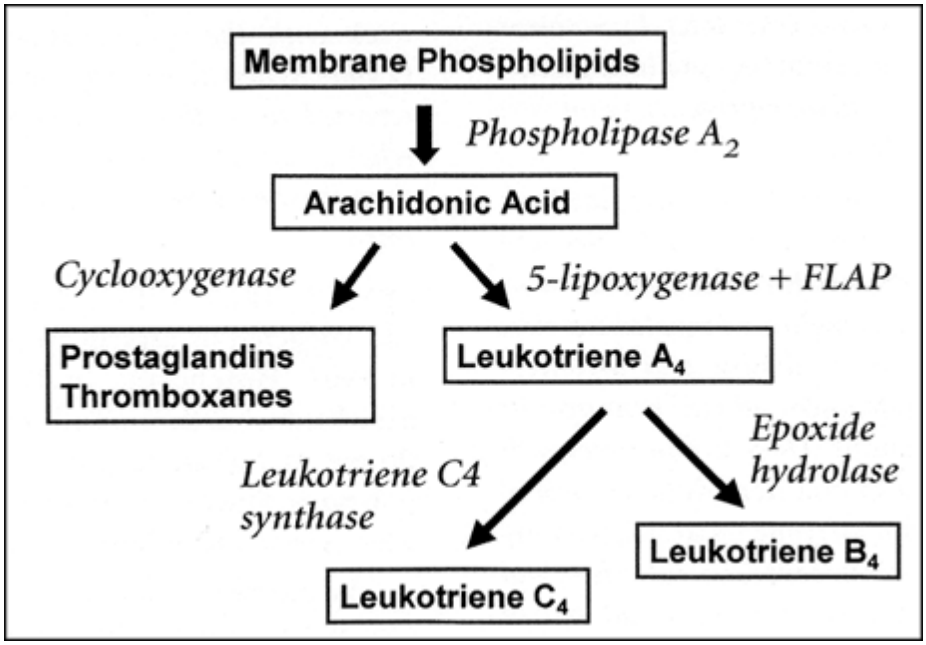
Importance of leukotrienes:

Leukotrienes are regulators of:

1. Anaphylaxis (the immediate hypersensitivity reaction): they are components of the complex called slow-reacting substance – A (SRS-A) that is involved in bronchial spasm.
2. Allergic reactions: LK C_4 , LK D_4 and LK E_4 have the effect of increasing vascular permeability and stimulating mucus secretion
3. Inflammation.
4. " Weal and flare" reaction of the skin.

- There are some approaches to anti-leukotriene drug development:
  - 5-LOX inhibitors such as **zileuton**.
  - Leukotriene-receptor antagonists such as **zafirlukast and montelukast**.
  - Phospholipase A_2 inhibitors such as corticosteroids.


COOH
Arachidonic acid
O2
5-lipoxygenase
OOH
COOH
5-HPETE
OH
COOH
peroxidase
5-HETE
H2O
O
leukotriene A4
+GSH → C4
+Glycyl-Cys → D4
+Cys → E4
Conversion of arachidonic acid to leukotrienes of series 4 (Group 2)



Synthesis of eicosanoids from arachidonic acid

* **FLAP: Five-lipooxygenase activating protein is a protein necessary for activation of LOX-5 in human**