EICOSANOIDS (LIPID DERIVED PRODUCTS)

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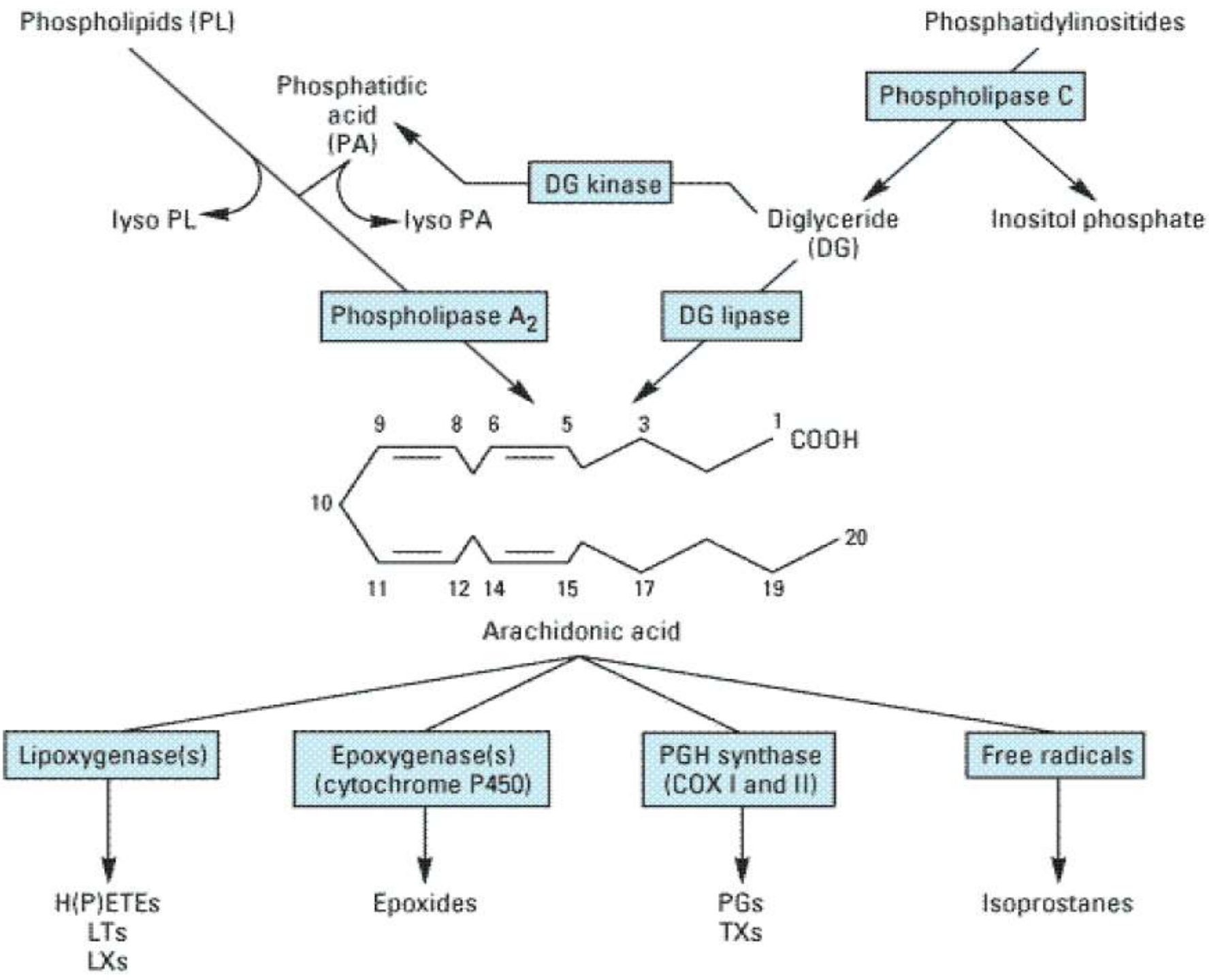
DEFINATION OF EICOSANOIDS

Eicosanoids are oxygenation products of polyunsaturated long chain fatty acids. These are mainly derived from arachidonic acid (AA) and other 20 carbon fatty acids released from cell membranes.

- Upon physical or chemical stimuli, AA is released from membrane phospholipids by either combination of phospholipase C and diglyceride lipase **OR** by one or more lipases of the phospholipase A2 (PLA2) and these are:

  1. cardiac PLA2 ,
  2. cytosolic PLA2, and
  3. secretory PLA2


Phospholipids (PL)
Phosphatidylinositides
Phosphatidic acid (PA)
Phospholipase C
DG kinase
lyso PL
lyso PA
Diglyceride (DG)
Inositol phosphate
Phospholipase A2
DG lipase
9
8
6
5
3
1
COOH
10
20
11
12
14
15
17
19
Arachidonic acid
Lipoxygenase(s)
Epoxygenase(s) (cytochrome P450)
PGH synthase (COX I and II)
Free radicals
H(P)ETEs
LTs
LXs
Epoxides
PGs
TXs
Isoprostanes

SYNTHESIS OF EICOSANOIDS

A. Cyclooxygenases (COXs) :

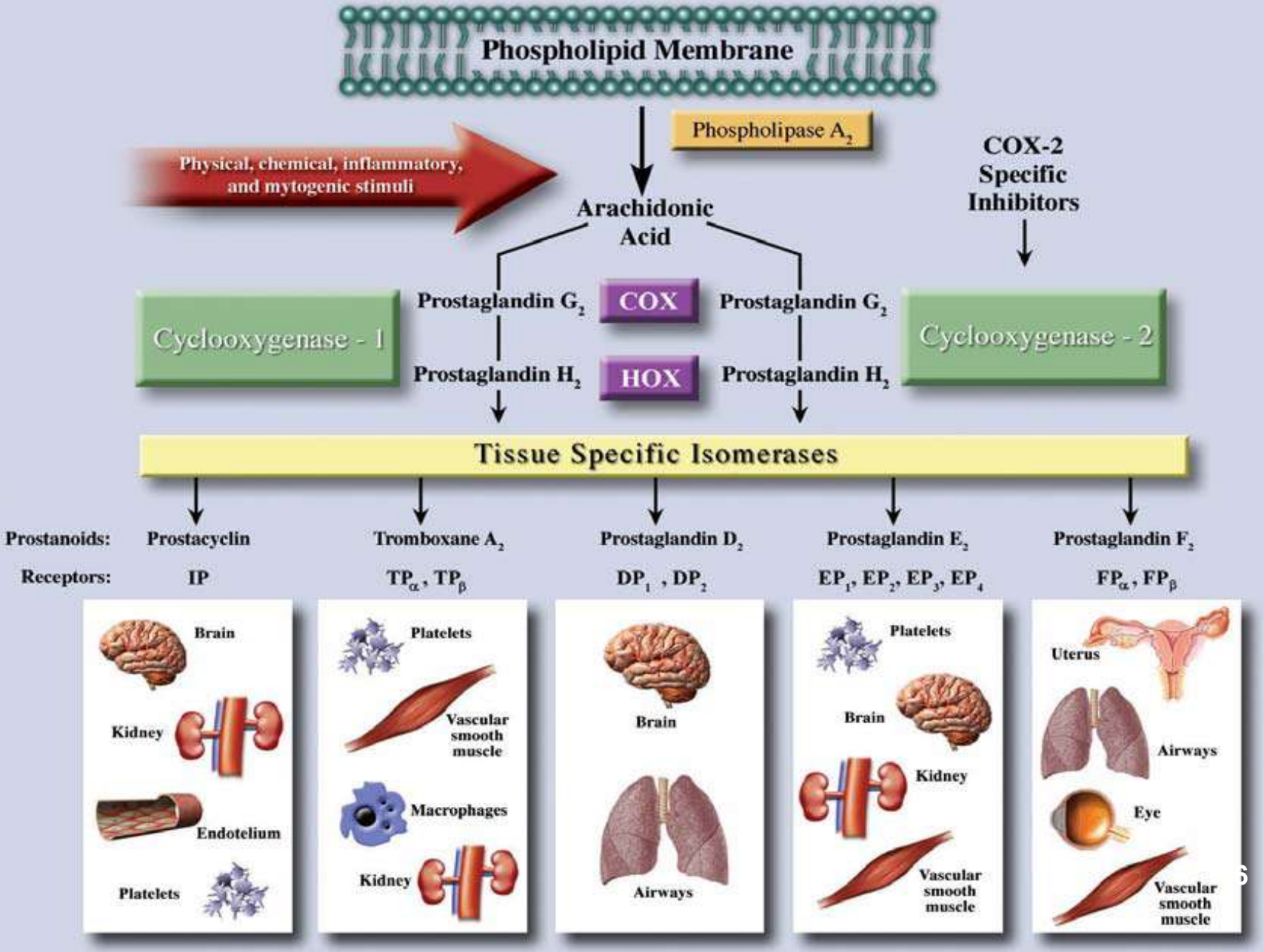
- This leads to formation of cyclic endoperoxides (PGG_2, PGH_2); then other tissue isomerases convert these endoperoxides to either Prostaglandins (PGs) such as (PGE_2, PGF_{2a} or PGD_2) or to Thromboxane A_2 (TXA_2) or Prostacyclin (PGI_2).

Tissues vary in their content or ability to synthesize PGs.

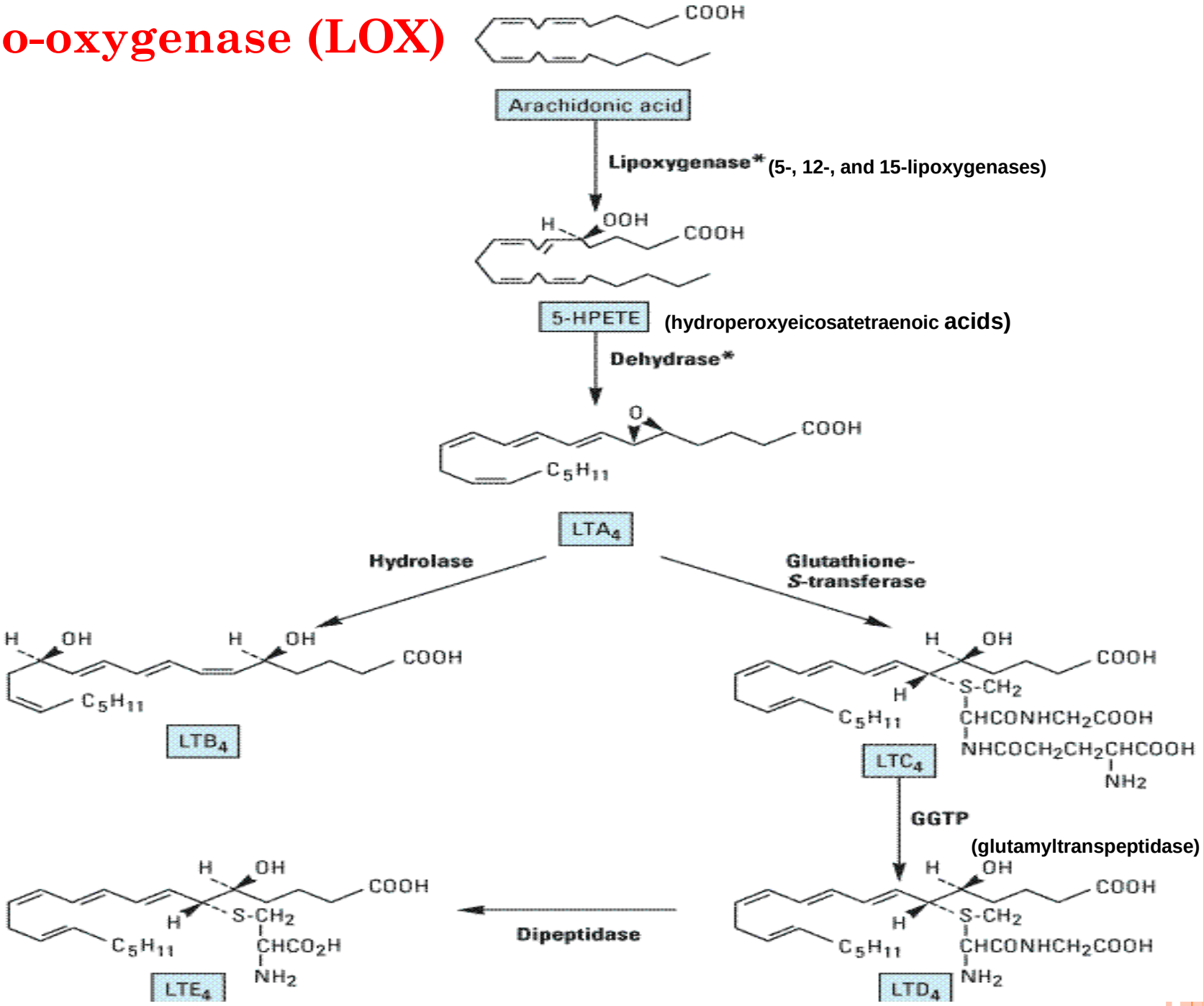
- Platelets: TXA_2 (vasoconstrictor + platelet aggregator)

- Endothelium: PGI_2 (vasodilator + inhibitor of platelet aggregation)

- Stomach: PGE_2 and PGI_2 decrease gastric acid secretion ; also have cytoprotective action by
  1. Increase mucus + $HCO3^-$ production
  2. Increase mucosal blood flow .


Phospholipid Membrane
Phospholipase A2
Physical, chemical, inflammatory, and mytogenic stimuli
Arachidonic Acid
COX-2 Specific Inhibitors
Cyclooxygenase - 1
Prostaglandin G2
COX
Prostaglandin G2
Cyclooxygenase - 2
Prostaglandin H2
HOX
Prostaglandin H2
Tissue Specific Isomerases
Prostanoids:
Prostacyclin
Tromboxane A2
Prostaglandin D2
Prostaglandin E2
Prostaglandin F2
Receptors:
IP
TPα, TPβ
DP1 , DP2
EP1, EP2, EP3, EP4
FPα, FPβ
Brain
Kidney
Endothelium
Platelets
Platelets
Vascular smooth muscle
Macrophages
Kidney
Brain
Airways
Platelets
Brain
Kidney
Vascular smooth muscle
Uterus
Airways
Eye
Vascular smooth muscle

B. Lipo-oxygenase (LOX)



- The most actively investigated leukotrienes are those produced by the 5-lipoxygenase present in inflammatory cells (basophils, mast cells, eosinophils, macrophages).

- This pathway is of great interest since it is associated with asthma and anaphylactic shock.

- Stimulation of these cells elevates intracellular Ca2+, and releases arachidonate; incorporation of molecular oxygen by 5-lipoxygenase then yields the unstable epoxide **leukotriene A4 (LTA4).**

- This intermediate either converts to the dihydroxy leukotriene B4 (LTB4) or conjugates with glutathione to yield leukotriene C4 (LTC4), which undergoes sequential degradation of the glutathione moiety by peptidases to yield LTD4 and LTE4.

- LTB_4 is powerful chemotactic & activator of neutrophils. It also stimulate proliferation & differentiation of T and B lymphocytes

- LTC_4 & D_4 are powerful chemotactics and activators of eosinophils and macrophages; they also cause bronchospasm (LTD_4), and increase mucus secretion and capillary permeability

EFFECTS OF PROSTAGLANDINS &THROMBOXANES

1. Smooth muscle:

A. Vascular:

- $PGF_{2\alpha}$ and TXA_2 cause vasoconstriction
- PGE_2 and PGI_2 cause vasodilation. PGI_2 is more potent (x 5) than PGE_2 in lowering blood pressure.
- PGE_2 maintains the patency of ductus arteriosus during pregnancy.

B. Gastrointestinal Tract:

- PGE_2 and PGI_2 are cytoprotective in stomach and decrease gastric acid secretion

C. Airways:

- Respiratory smooth muscle is relaxed by PGD2, PGE1, PGE2, and PGI2 (bronchodilation) and contracted by TXA2 and $PGF_{2\alpha}$ (bronchospasm).

2. Platelets :

- TXA_2 causes platelets aggregation while PGI_2 inhibits it.

3. Renal:

- PGE1, PGE2, and PGI2 increase glomular filtration through their vasodilating effects. These prostaglandins also increase water and sodium excretion.
- TXA2 causes intrarenal vasoconstriction resulting in a decline in renal function

4.Genital system :

- PGE_2 in semen is produced by the seminal vesicles, and it increases the viability of spermatozoa. Its level is increased by testosterone, and is decreased in infertile semen.

- In female, PGE_2 is involved in primary dysmenorrhea and in the onset of labour.

5. Central and Peripheral Nervous Systems:

- PGE1 and PGE2 increase body temperature. Pyrogens release interleukin-1, which in turn promotes synthesis and release of PGE2.
- PGE compounds inhibit the release of norepinephrine from postganglionic sympathetic nerve endings.

6. Neuroendocrine Organs:

- PGE compounds promote the release of growth hormone, prolactin,TSH, ACTH, FSH, and LH.

7. Bone Metabolism:

- PGE2 increases bone turnover, ie, stimulation of bone resorption and formation.

8. Eye:

- PGE and PGF derivatives lower the intraocular pressure. This is probably due to increased outflow of aqueous humor from the anterior chamber

CLINICAL USES OF PGs:

1. PGE_2 (Dinoprostone): used for

Induction of abortion or labour.
Enhance labour.
Stop post partum hemorrhage.

All are given intra-vaginal or IV infusion.

2. PGI_2 (Epoprostenol): is sometime used by IV infusion for primary pulmonary hypertension, and to protect platelets during hemodialysis

3. PGE_1 analogue (Alprostadil): is useful as urethral suppositories for male impotence, and sometimes IV to maintain patency of ductus arteriosus in some forms of congenital heart disease

4. PGE_1 analogue (Misoprostol): is given orally to prevent peptic ulcer due to NSAIDs , and sometimes for induction of abortion

5.$PGF_{2\alpha}$ analogue (Latanosert): is used as eye drops to increase drainage of aqueous humor and decrease the intraocular pressure in glaucoma

CLINICAL PG ANTAGONISTS

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) : inhibit cyclooxygenase COX, so decrease production of PGs, TXA_2, and prostacyclin. LTs are not affected.

Two types of COX :

1. COX 1 : constitutional , and are protective in many tissues e.g. G.I.T , kidneys, platelets
2. COX 2 : inducible; produced by inflammatory cells (macrophages, eosinophils, mast cells, NOT by neutrophils.) at sites of inflammation

CLINICAL LT INHIBITORS

Clinically useful LT inhibitors used for **asthma prophylaxis** include :

1. **Zileuton : 5-LOX inhibitor** that decrease LTs synthesis
2. **Zafirleukast & Monteleukast:** LT receptor antagonists

Thanks