DOCTOR 2020 | JU

METABOLISM

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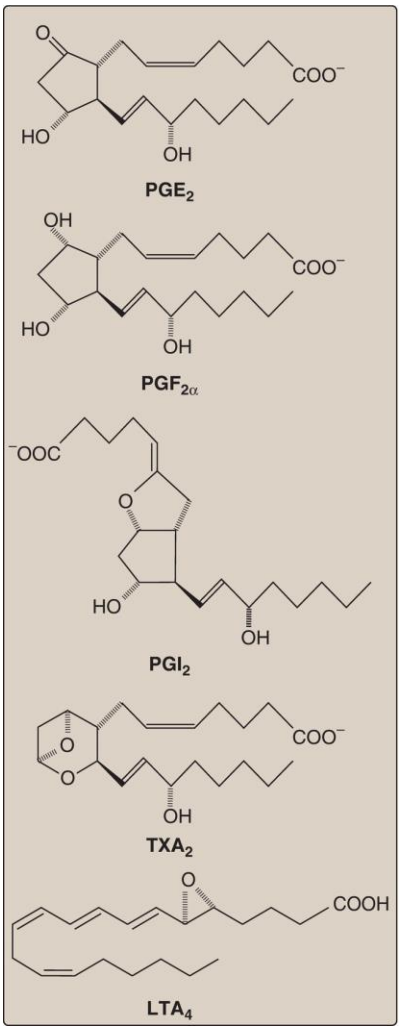
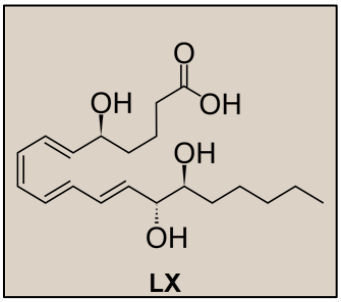
Eicosanoids

- Eicosanoids are 20 carbon molecules derived mainly from Arachidonic Acid (AA).



- **Eicosanoids are classified into four groups: (1) Prostaglandins (PG) and prostacyclins (PGI), and (2) thromboxanes (TX); a third type is the leukotrienes (LT) and a fourth is and lipoxins (LX).**
  - **Prostaglandins and thromboxanes are known as prostanoids.**
- **They are produced from ω-3 and ω-6 polyunsaturated FA with 20 carbons (eicosa = 20).**
  - From essential fatty acids like: linoleic fatty acids
- **They elicit physiologic (inflammatory) and pathologic (hypersensitivity) responses:**
  - **Gastric integrity, renal function, smooth muscle contraction (intestine and uterus), blood vessel diameter (dilation and constriction), and platelet homeostasis.**
- **They are not stored.**
- **They have a short half-life.**
- **They are rapidly metabolized to inactive products.**
  - They are not considered hormones even though they act like them, because they aren't stored and they work in the vicinity (in the neighborhood of cells) and locally (they don't travel in the blood).

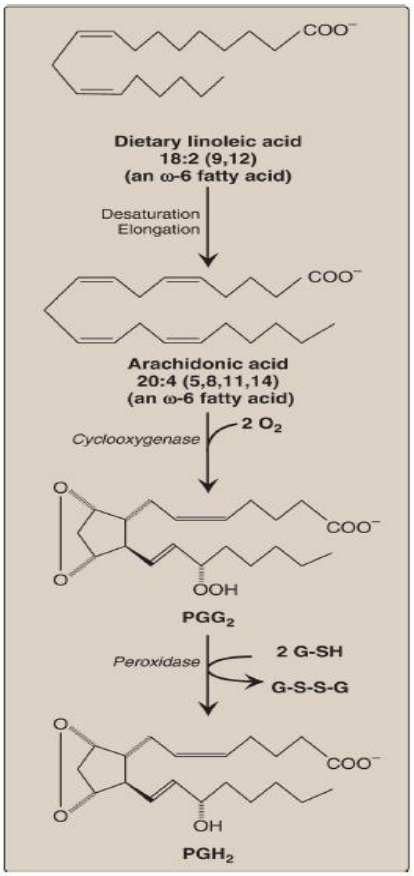


Reasons for naming

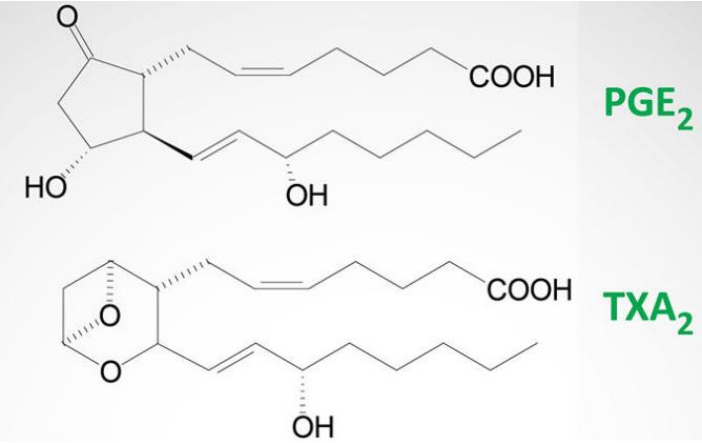
- **Site of synthesis:**
  - **Prostaglandins were originally shown to be synthesized in the prostate gland then it turned out that they're produced by different tissues.**
  - **Thromboxanes from platelets (thrombocytes: name of platelets)**
  - **Leukotrienes from leukocytes.**
  - **Lipoxins are inflammation resolving eicosanoids synthesized through lipoxygenase interactions.**

Synthesis from arachidonic acid

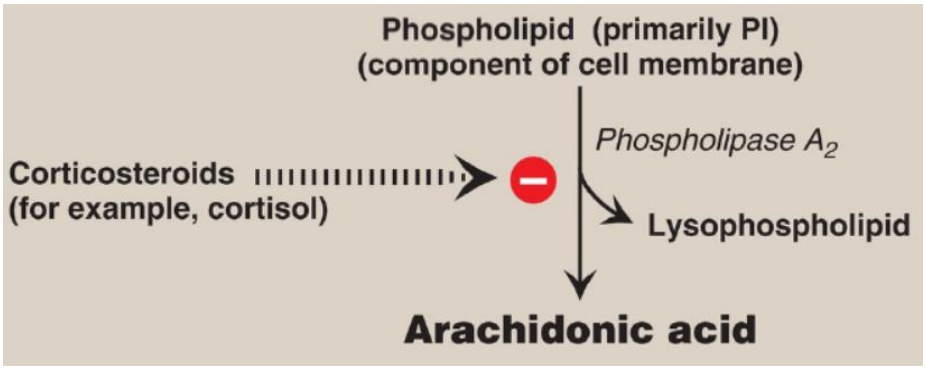
- **Arachidonic Acid (an eicosatetraenoic FA), is the immediate precursor of PG (AKA series 2 or those with two double bonds).**
- **AA is derived by the elongation (addition of acetyl CoA) and desaturation of the linoleic acid.**
- **AA is incorporated into membrane phospholipids (typically PI) at carbon 2 and released by *phospholipase A2.***
- **Remember PI (Phosphatidylinositol) composed of glycerol backbone + stearic acid on C1 + AA on C2 + inositol group on C3**

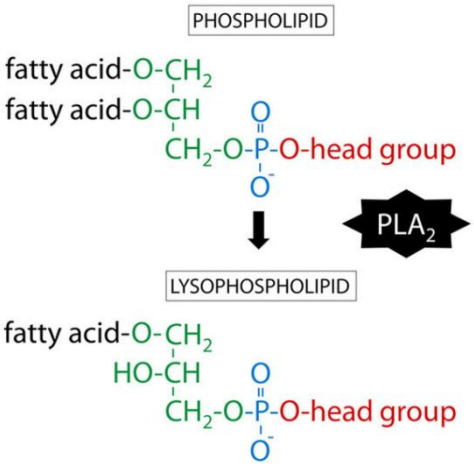


Prostaglandins and thromboxanes



- **Prostaglandins (PG) are found in most tissues and organs and are produced by almost all nucleated cells.**
- **They have a cyclopentane ring.**
- **They are designated by a letter that describes the ring modification followed by a number that indicates the number of double bonds.**
- **Series 1 PGs contain one double bond, series 2 has 2, and so on.**
- **Thromboxanes have a 6-membered ring.**

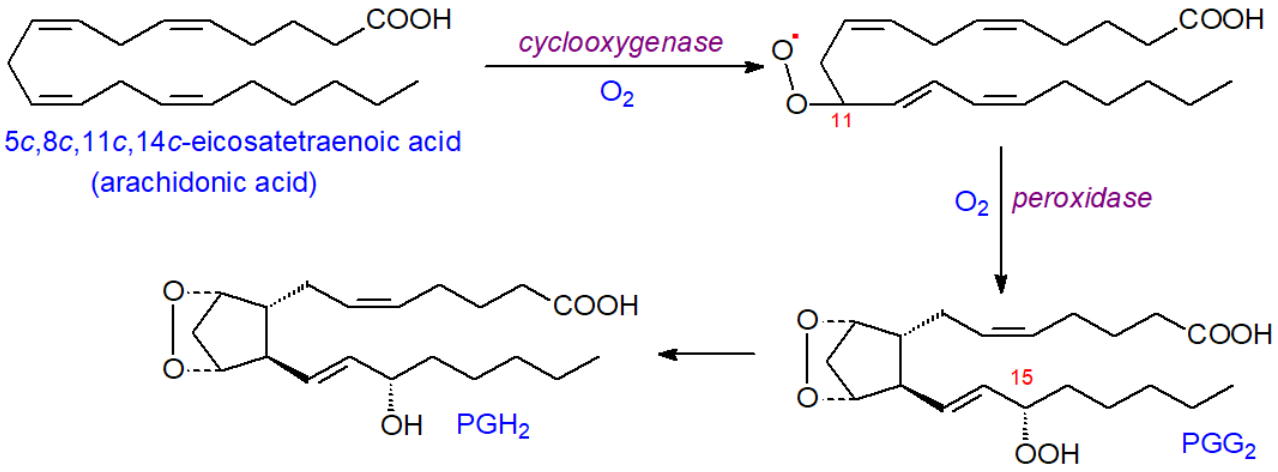




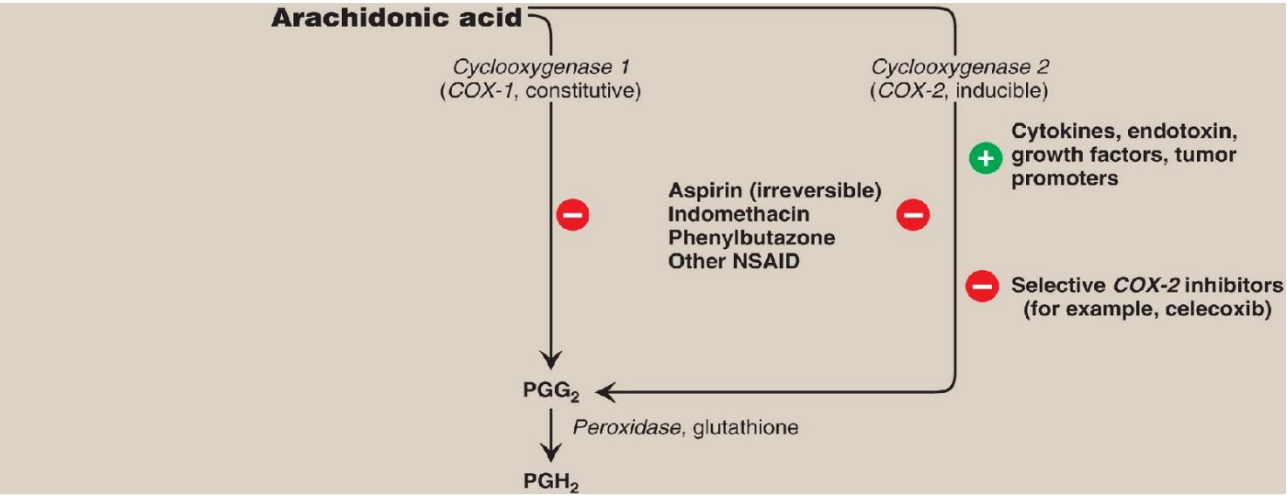
- **As we mentioned AA is produced from PI by Phospholipase A_2**
- **Phospholipase A_2 is inhibited by Corticosteroids (e.g. cortisol), that's why cortisol is considered an anti-inflammatory compound because it blocks the production of AA (which is considered an inflammatory molecule).**

Prostaglandin H2 synthase

- **Synthesis of PGs and TXs starts by oxidative cyclization of arachidonic acid to yield PGH2 by PGH2 synthase (or, prostaglandin endoperoxide synthase)**
- **The PGH2 synthase is ER membrane-bound protein and has two catalytic activities: fatty acid cyclooxygenase (COX), which requires two molecules of O2, and peroxidase, which requires reduced glutathione and O2.**



- **There are two isozymes of PGH2 synthase: COX-1 and COX-2.**

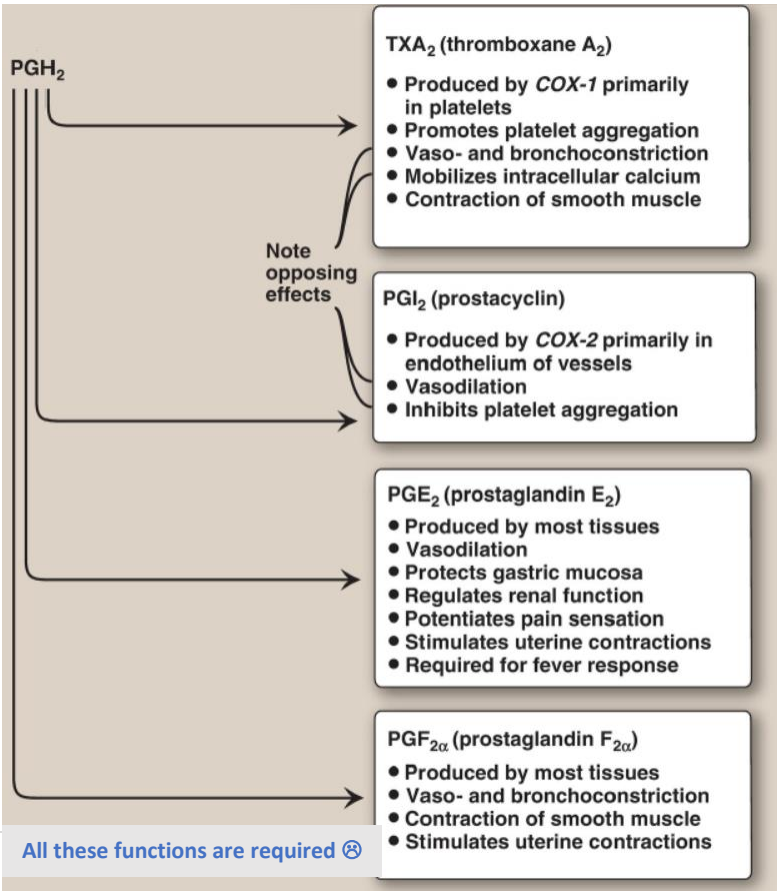


Notice the activators and inhibitors ↑↑

- **COX-1 is made constitutively in most tissues and is involved in functions of gastric and renal tissues and platelet aggregation.**
- **COX-2 is found in specific tissues, it's inducible, and mediates the pain, heat, redness, and swelling of inflammation and the fever of infection.**
- **Both COX-1 and COX-2 catalyze the two reactions.**
    - **Aspirin** targets both COX-1 and COX-2 by **acetylation** the Cyclooxygenase activity thus preventing the PG formation and its considered as anti-inflammatory drug, but COX-1 is involved in functions of gastric and renal tissues so **Aspirin** has badly side effects, to solve this problem scientists manufacture a selective inhibitory drug for COX-2 such as **celecoxib** , so **celecoxib** is considered an anti-inflammatory because it acts on COX-2 only, but COX-1 is involved in platelet aggregation, so there is a benefit of **Aspirin** which is preventing platelet aggregation although it has a badly side effects.
    - Celecoxib and other COX-2 inhibitors considered as anti-inflammatory but they don't prevent the platelet aggregation.

PGH2 is then converted to a variety of PG and TX

- **From the production of PGH2, all eicosanoids can be produced expect of leukotrienes and lipoxins.**
- **The opposing effects of TXA2 and PGI2 limit thrombi formation to sites of vascular injury.**
- **Aspirin has an antithrombogenic effect. It inhibits TXA2 synthesis by COX-1 in platelets and PGI2 synthesis by COX-2 in endothelial cells**

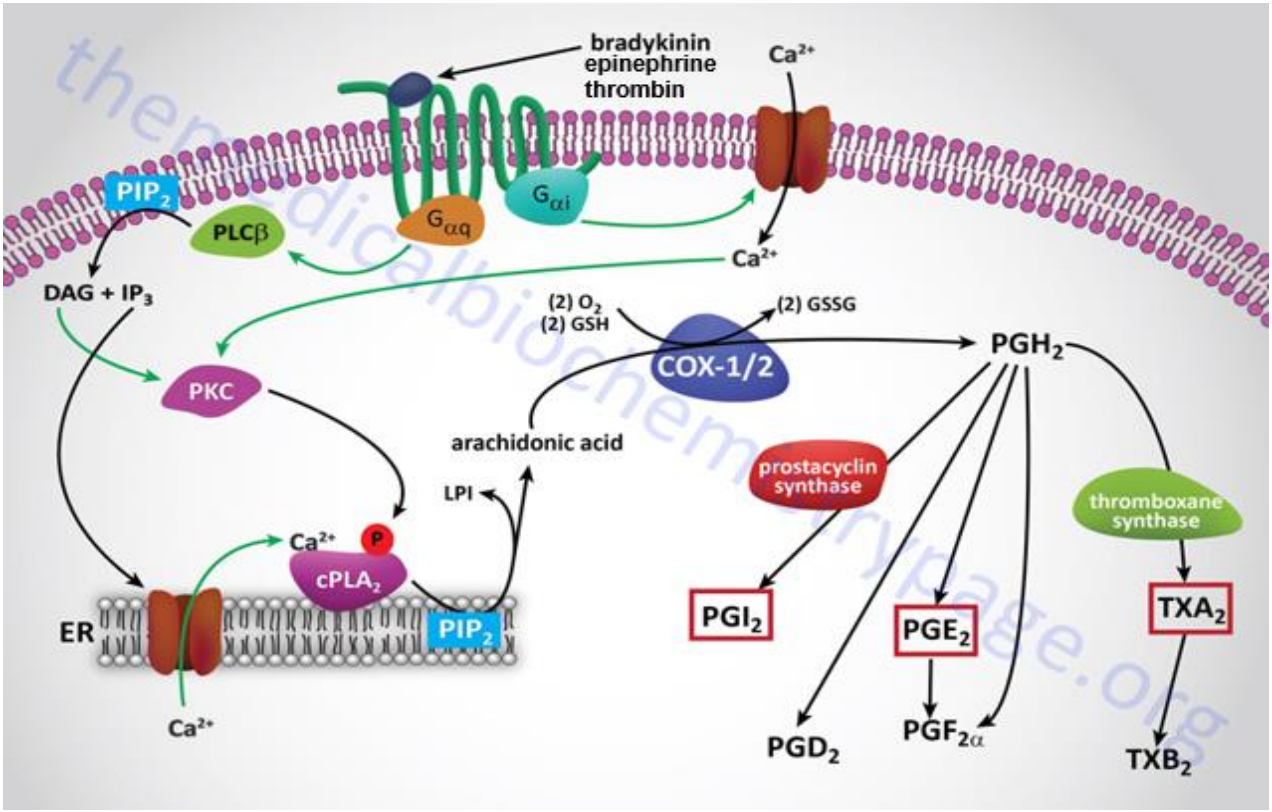


All these functions are required ☹

- **COX-1 inhibition cannot be overcome in platelets because they cannot synthesize it anymore, but COX-2 inhibition can be overcome in endothelial cells.**
- **This difference is the basis of low-dose aspirin therapy used to lower the risk of stroke and heart attacks by decreasing formation of thrombi**

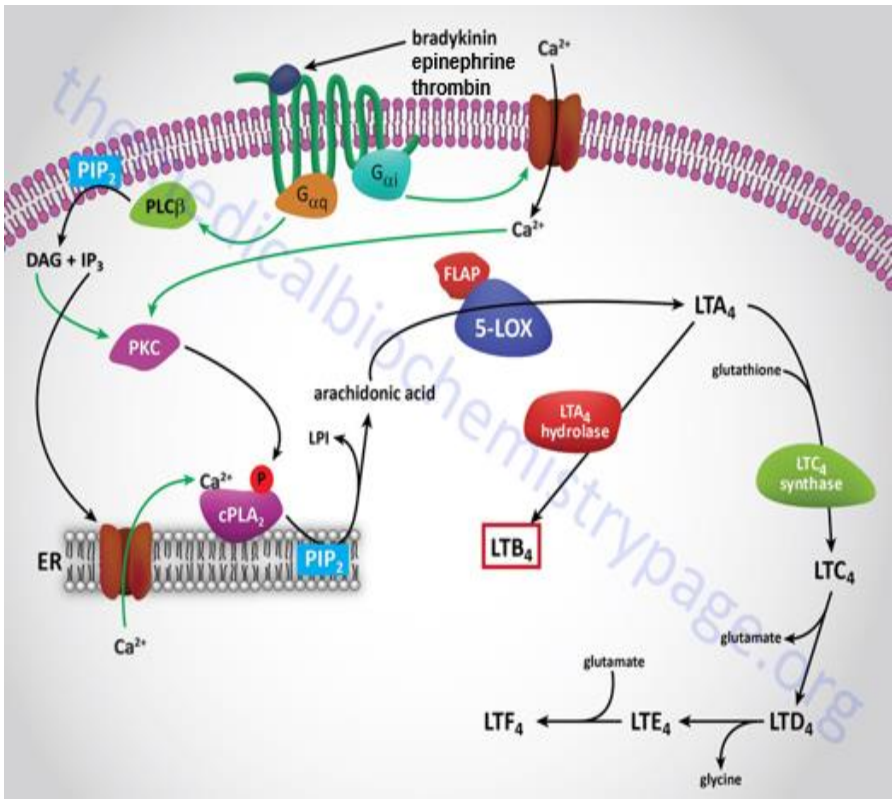
Signalling

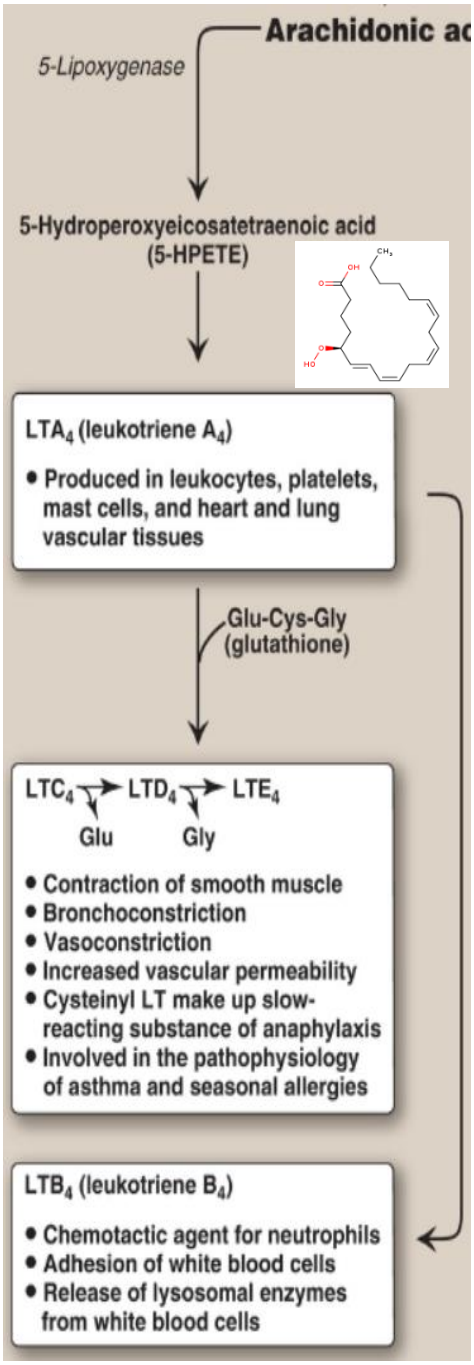
- How these PGs are produced?
- Inflammatory molecules such as bradykinin, epinephrine and thrombin bind to a GPCR that is linked to Gαi and Gαq, Gαi open Ca^{+2} channels and Gαq activates PLCβ (phospholipase C β) which produce DAG and IP3 from PIP2, IP3 open Ca^{+2} channels in the ER, Dag simulates PKC, Ca^{+2} with PKC stimulate PLA2 (phospholipase A2) and produce AA (remember: from PI), AA is converted to PGH2 by COX-1/2, PGH2 is the precursor for the other PGs (PGI2, PGE2 …….)



Leukotriene synthesis

Like the PG but instead of COX-1/2 we have 5-Lipoxygenase (5-LOX) that convert AA to leukotriene A4 (LTA4)





Notes:

1-LOX-5 produce (5-HEPTE) as intermediate then LTA A4.

2- We need GSH to produce the other leukotrienes LTC4, LTD4…….

3-Functions are required.

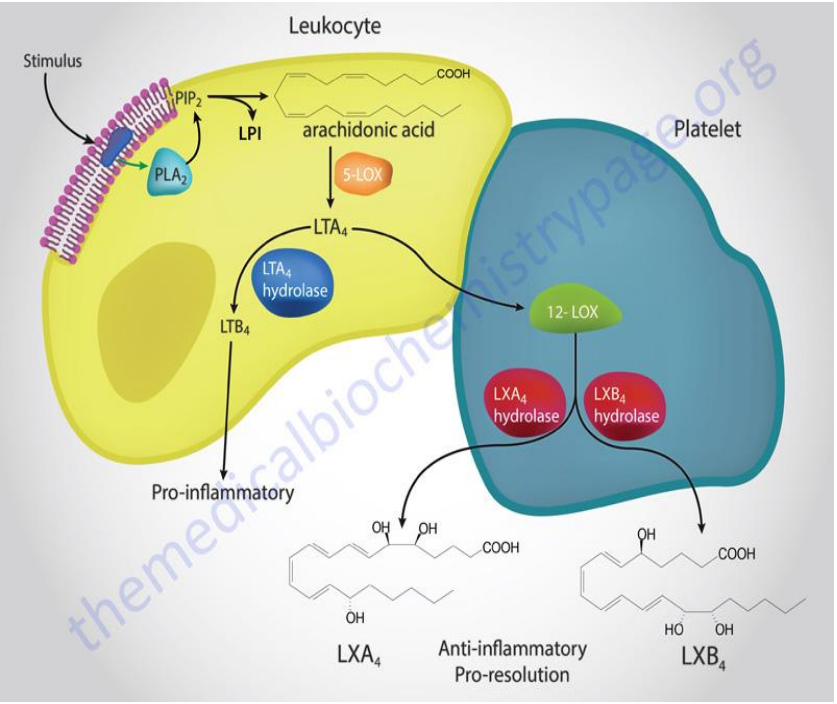
Catabolism of prostanoids

- **Prostanoids are often deactivated quickly either spontaneously or enzymatically.**
  - **Half-lives of 30 seconds.**
- **Prostanoids are first transported from the extracellular fluid to the cytoplasm by the prostaglandin transport protein (PGT) where they are converted into products that are either inactive or can inhibit cell proliferation.**
- **They are eliminated via the kidney into the urine.**

صلّ على النبي

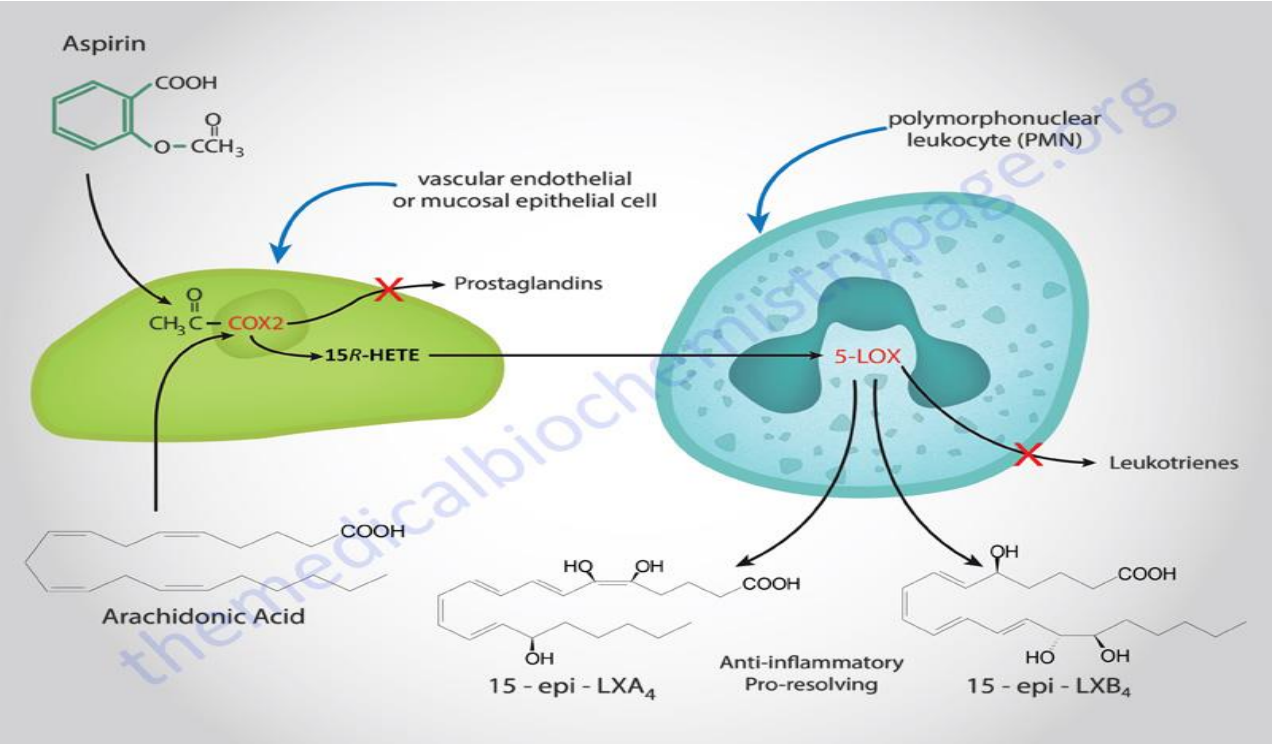
Synthesis of lipoxins

- **The lipoxins are anti-inflammatory since they inhibit the actions of the leukotrienes.**
- **Synthetic pathways of lipoxins:**
  - **The "classic" pathway: 5-lipoxygenase (5-LOX) in leukocytes followed by 12-LOX in platelets.**
  - **The second pathway 15-LOX in epithelial cell, such as airway cells, followed by 5-LOX action in leukocytes.**
  - **The third pathway: aspirin-mediated acetylation of COX-2.**



How does aspirin do that? (Third pathway)

- **Aspirin-induced acetylation of COX-2 alters the enzyme such that it converts arachidonic acid to 15*R* hydroxyeicosatetraenoic acid (15*R*-HETE), which is then rapidly metabolized to the epi-LXs in monocytes and leukocytes by 5-lipoxygenase (5-LOX).**

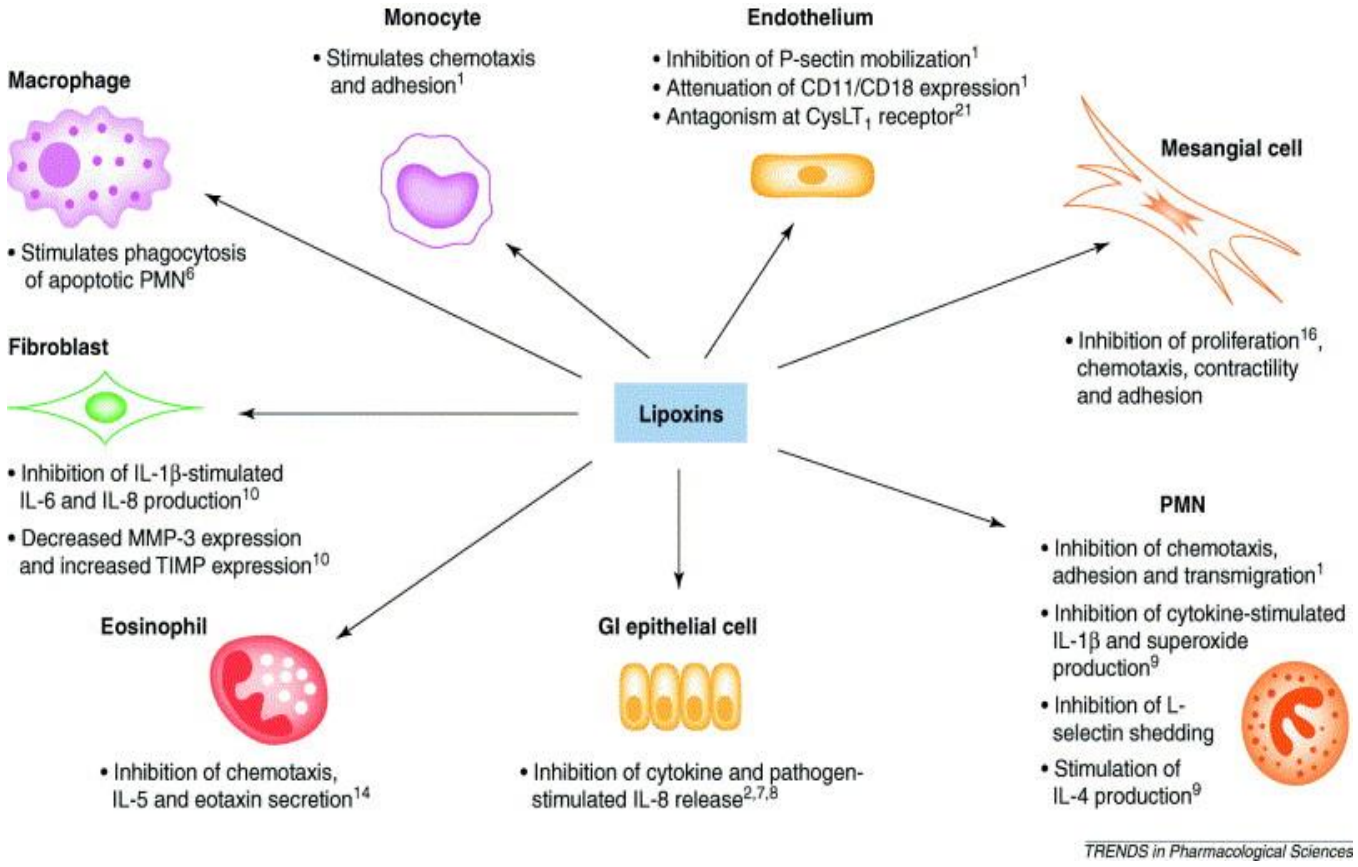


The functions of lipoxins

- **The lipoxins LXA_4 and 15 epi-LXA_4 function through ALXR, a G protein-coupled receptor (GPCR) to:**
  - **promote the relaxation of the vasculature,**
  - **inhibit polymorphonuclear leukocyte (PMN) chemotaxis, PMN-mediated increases in vasopermeability, and PMN adhesion and migration through the endothelium.**
  - **stimulate phagocytosis of apoptotic PMNs by macrophages (the resolution phase of inflammatory events).**

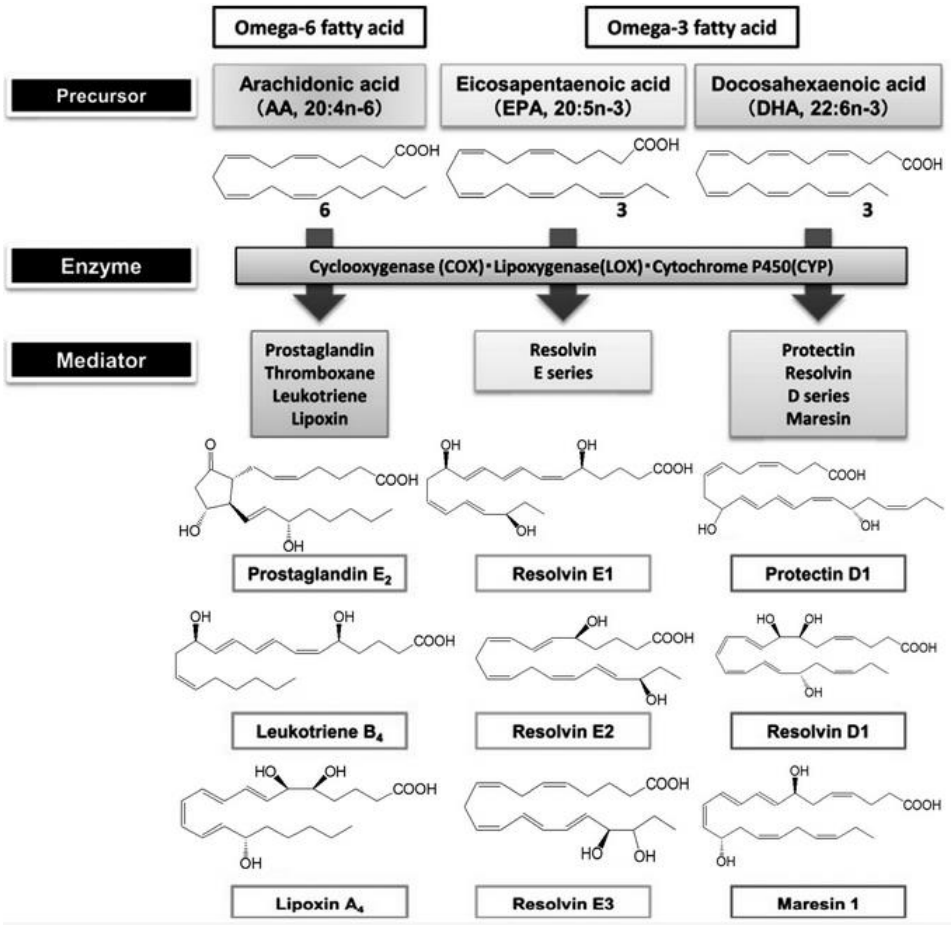
- **blocking expression of the pro-inflammatory IL-8 by macrophages and endothelial.**
- **regulate the actions of histamine leading to a reduction in edema.**
- **Increasing the production of prostacyclin (PGI_2) and nitric oxide (NO).**

The functions of lipoxins (in picture)



The specialized pro-resolving mediators (SPM)

- **Resolvins (Rv), protectins (PD), and maresins (MaR) are EPA- and DHA-derived bioactive metabolites that are anti-inflammatory lipids.**
- **Aspirin triggers their synthesis.**
- **They stimulate the resolution of the inflammatory responses through G protein-coupled receptors via diverse actions.**
  - **Resolvins share a17-hydroxyl group added by lipoxygenase, 15-LOX.**
  - **The neuroprotectin, (N)PD1, is derived from DHA (omega-3) by 15-LOX and then enzymatic hydrolysis.**
  - **The macrophage mediator resolving inflammation molecules (maresins), MaR1 and MaR2, are derived by 12-LOX on DHA.**



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