فريق طوفان الأقصى

METABOLISM

Modified N. 12

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Metabolism of lipids VII:

Eicosanoids

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Resources

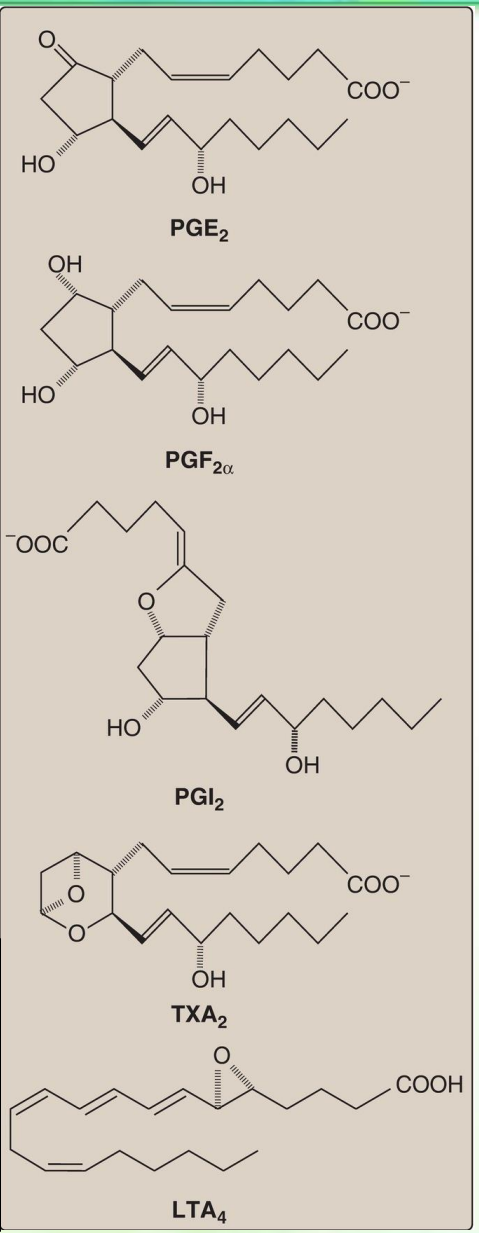
- This lecture
- Lippincott's Biochemistry, Ch. 17
- Eicosanoid Metabolism: Prostaglandins, Thromboxanes, Leukotrienes, and Lipoxins (https://themedicalbiochemistrypage.org/eicosanoid-metabolism-prostaglandins-thromboxanes-leukotrienes-and-lipoxins/)
- Bioactive Lipid Mediators of Inflammation (https://themedicalbiochemistrypage.org/bioactive-lipid-mediators-of-inflammation/)

Overview of eicosanoids

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

Do not memorize the structures

- Eicosanoids are classified into four groups: (1) Prostaglandins (PG) and prostacyclins (PGI), and (2) thromboxanes (TX); (3) the leukotrienes (LT) and (4) lipoxins (LX).
  - Prostaglandins, prostacyclins, and thromboxanes are known as prostanoids.
- They are produced from ω-3 and ω-6 polyunsaturated FA with 20 carbons (eicosa = 20). **NOTE:** AA produced from ω-3 —> primarily lipoxin.
- 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 (in relation to blood clotting).
- They are not stored.
- They have a short half-life.
- They are rapidly metabolized to inactive products.
- They are not hormones.



- **The complement in this slide:** Prostaglandins, prostacyclins, and thromboxanes are known as prostanoids. (the name of prostanoids is derived from prostate, when they were first discovered -especially prostaglandins and prostacyclins- they were found to be mainly produced by prostate but in fact they can be produced by different cells as well).
- The main physiologic function for eicosanoids is inflammation.
- The main pathological effect for eicosanoids (due to their overexpression) is hypersensitivity/ allergic reactions/ sever inflammatory response.
- Eicosanoids have a short half-life means they are produced and released immediately within seconds unlike hormones which generally have longer Half Lives because they need to travel longer distances sometimes when released into the blood (and that explains the sentence: they are not hormones).

- **NOTE:** the picture in the previous slide shows different structures of ecosanoids, they're not for memorization but when you see them you need to recognize that they are eicosanoids and you will learn how to recognize them later on.

Reasons for naming

- Site of synthesis:
  - Prostaglandins were originally shown to originate from the prostate gland.
  - Thromboxanes from platelets (thrombocytes)
  - Leukotrienes from leukocytes.
  - Lipoxins are inflammation resolving eicosanoids synthesized through **lipox**ygenase **in**teractions.

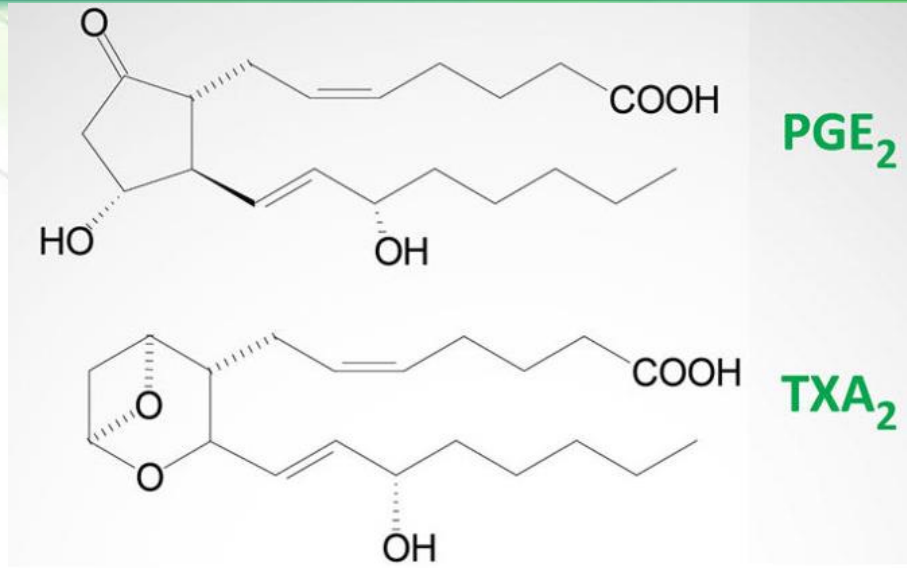
NOTE: **They are not important information for exam purposes, they are just for you to know where the names have arisen from.** 😊

Prostaglandins and thromboxanes

Do not memorize the table

TABLE 14.2: Salient features of prostaglandins

Name	*Substituent groups*
PGA	Keto group at C9; double bond C10 and 11
PGB	Keto group at C9; double bond C8 and 12
PGD	OH group at C9; keto group at C11
PGE	Keto group at C9; OH group at C11
PGF	OH groups at C9 and C11 (Fig.14.2)
PGG	Two oxygen atoms, interconnected to each other, and bonded at C9 and C11; hydroperoxide group at C15
PGH	Same ring as PGG; but C15 has OH group
PGI	Double ring. Oxygen attached to C6 and C9, to form another 5-membered ring. Hence called prostacyclin.



NOTE: PGE2 has a 5-membered ring while TXA2 has a 6-membered ring.

- Prostaglandins are produced by almost all nucleated cells in most tissues and organs.
- 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.

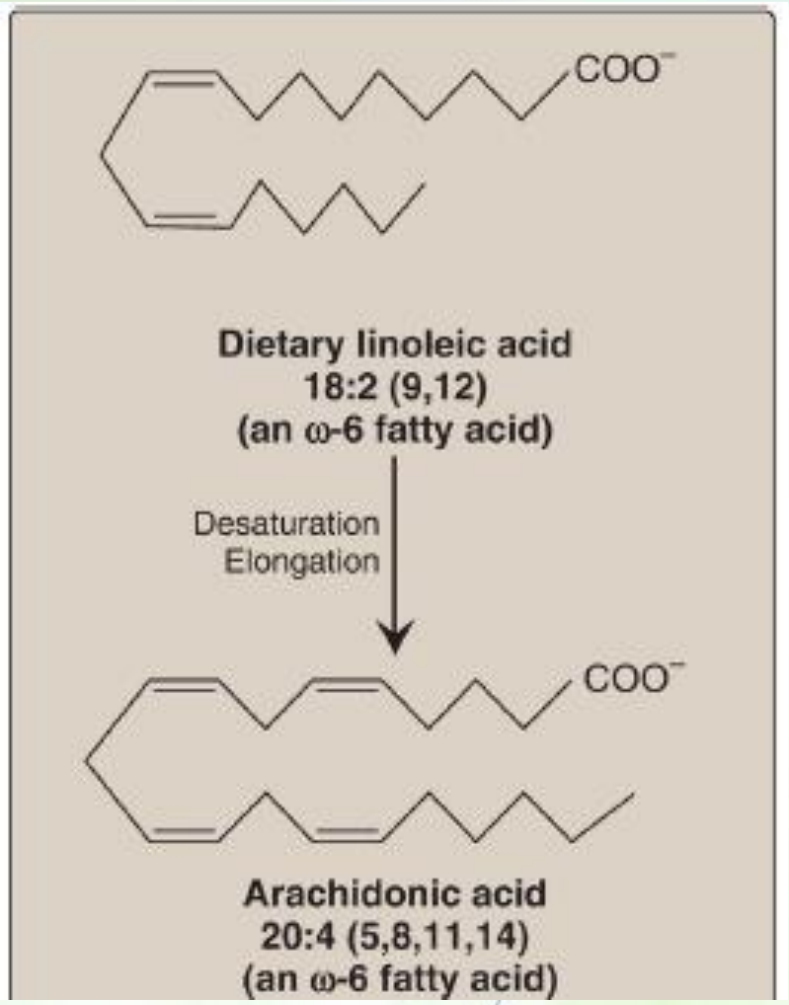
- **The complement in this slide:** the number 2 in TXA2 indicates that it has two double bonds so eicosanoids are classified accordingly into series, **series 1** which contain one double bond and **series 2** which contain two double bonds

- **NOTE:** the designations of their names (the letters and numbers) indicate certain chemical structures (keto group or hydroxyl group for example)

Synthesis from arachidonic acid

NOTE: linoleic acid—> arachidonic acid—> eicosanoids .

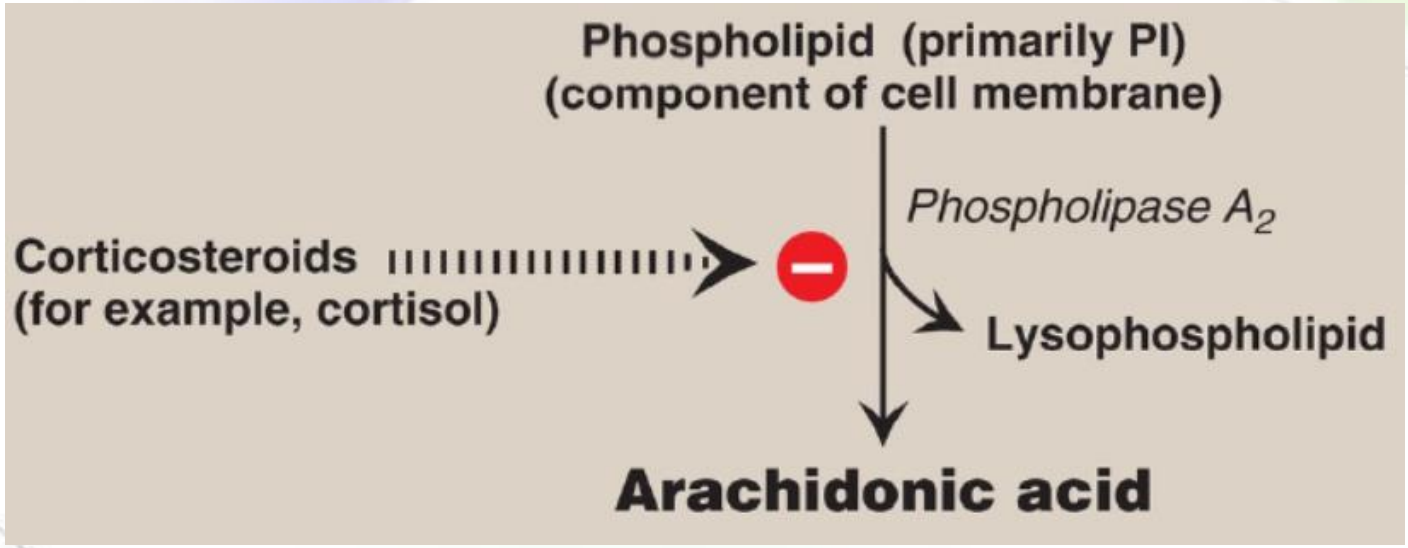
- Arachidonic acid (an eicosatetraenoic FA), is the immediate precursor of PG (AKA series 2 or those with two double bonds).
- Arachidonic acid is derived by the elongation (addition of 2 carbon molecules) and desaturation (addition of 2 double bonds: from 2 double bonds to 4 double bonds) of the linoleic acid.
- Arachidonic acid is incorporated into membrane phospholipids (plasma membrane or ER membrane) (typically PI) at carbon 2 and released by *phospholipase A2.*



NOTE: so PI is the storage place or the reservoir of Arachidonic acid.

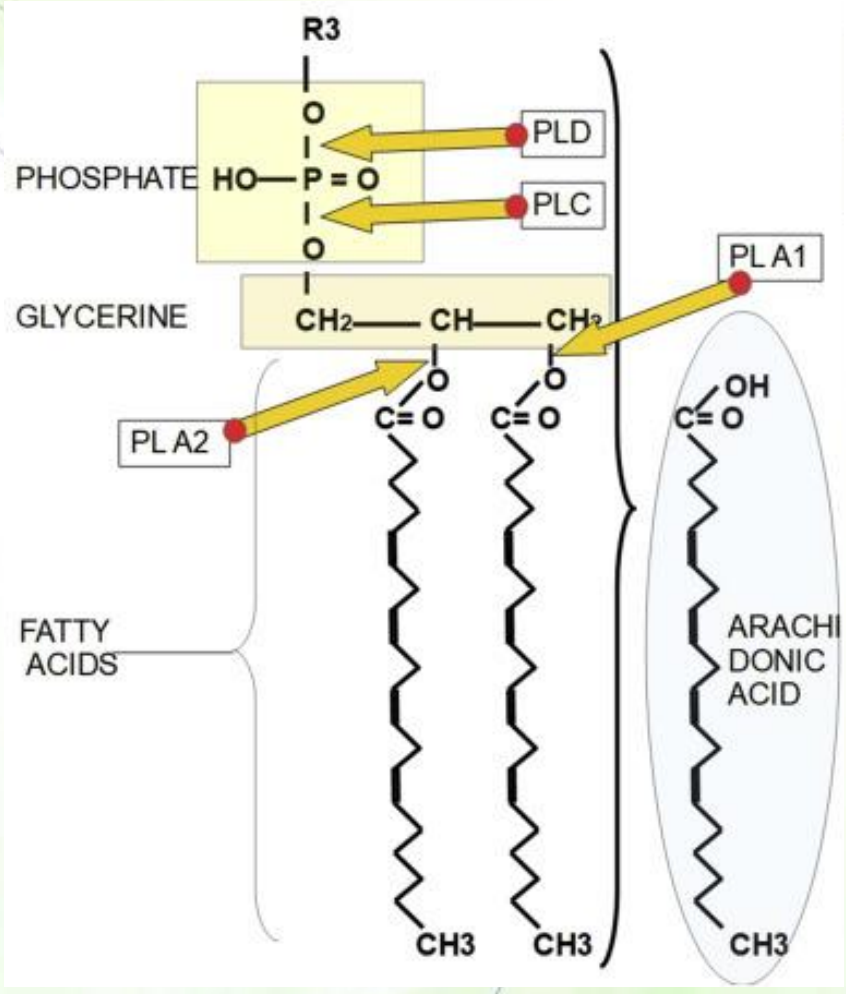
NOTE: 18:2 in linoleic acid: 18 C with 2 double bonds.

Before synthesis of PGs and TXs



- **NOTE:** As we mentioned AA is produced from PI by Phospholipase A2, Phospholipase A2 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).

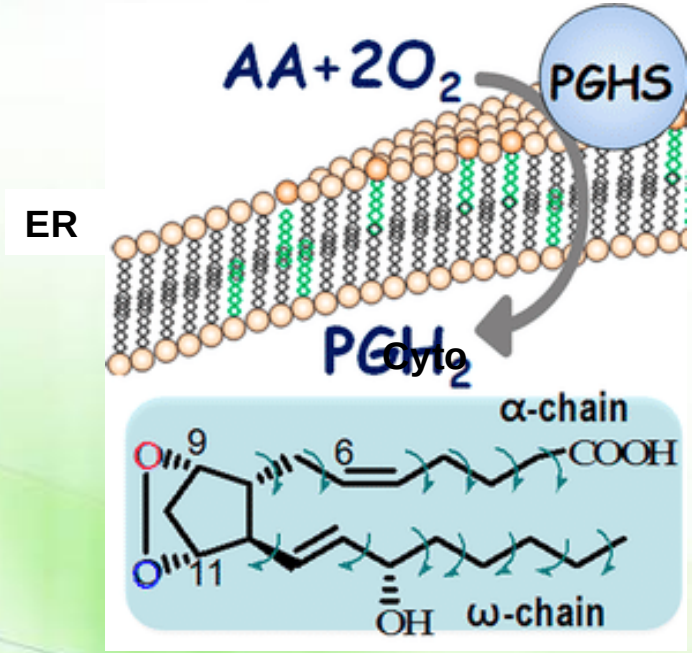
- **NOTE:** the picture to the right shows the locations or positions where different phospholipases act.

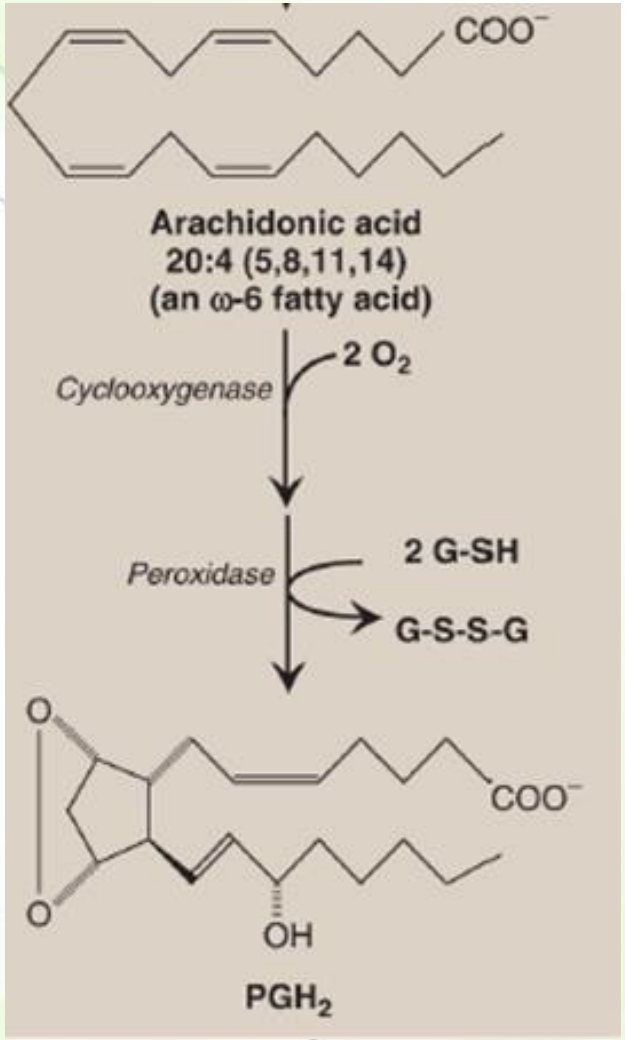


Prostaglandin H2 synthase

- Synthesis of PGs and TXs starts by oxidative cyclization of arachidonic acid to yield PGH2 by PGH2 synthase (or, prostaglandin endoperoxide synthase).
- PGH2 synthase has two catalytic activities: a fatty acid cyclooxygenase (COX) and a peroxidase, which requires reduced glutathione.

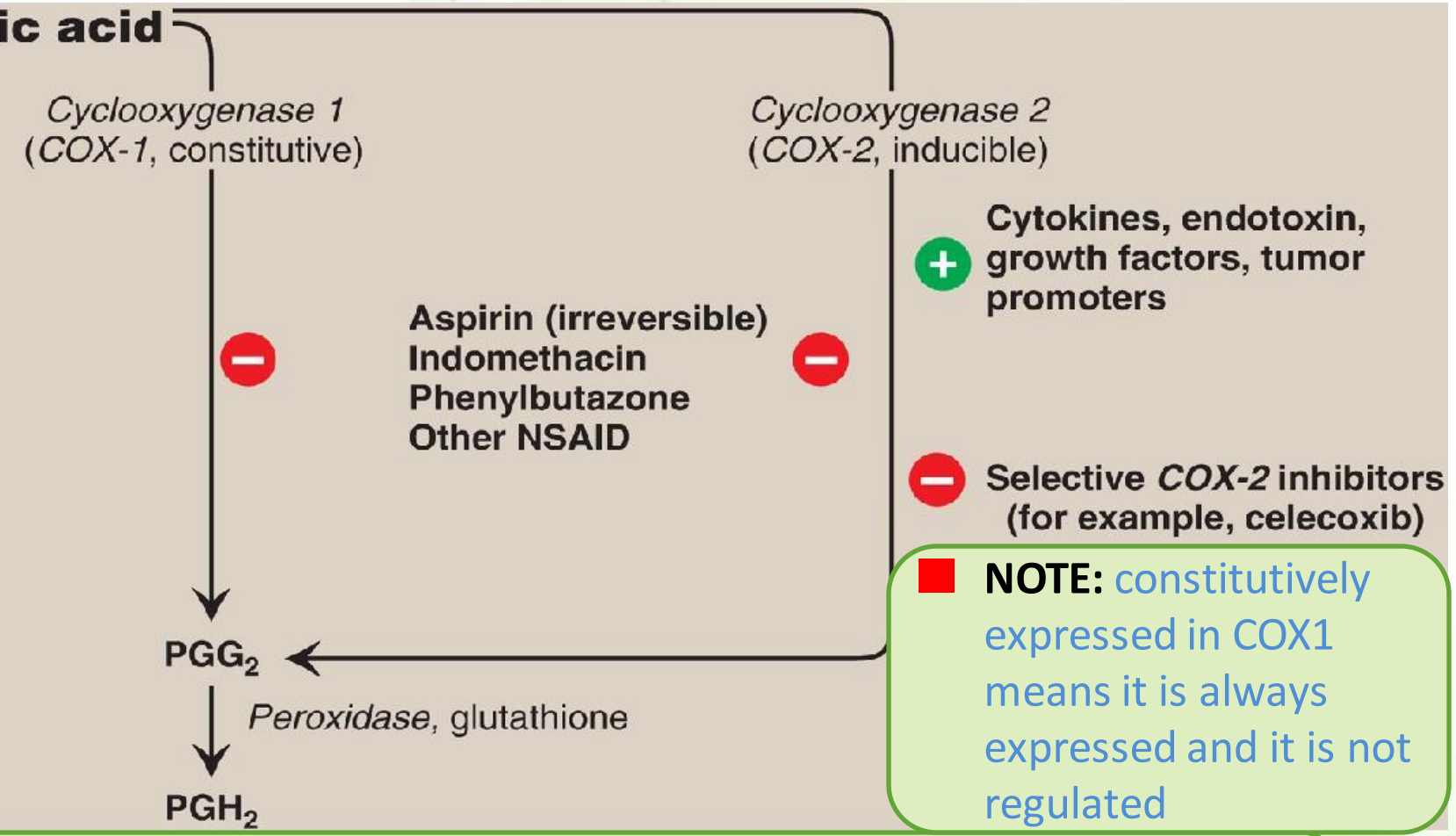
- **NOTE:** peroxidase needs 2 molecules of reduced glutathione.
- PGH2 is the first inflammatory eicosanoid.





Cyclooxygenases

- There are two isozymes of PGH2 synthase: COX-1 and COX-2.
- COX-1 is made constitutively in most tissues and affects platelet aggregation and the functions of gastric renal tissues.
- COX-2 is inducible in specific tissues 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.

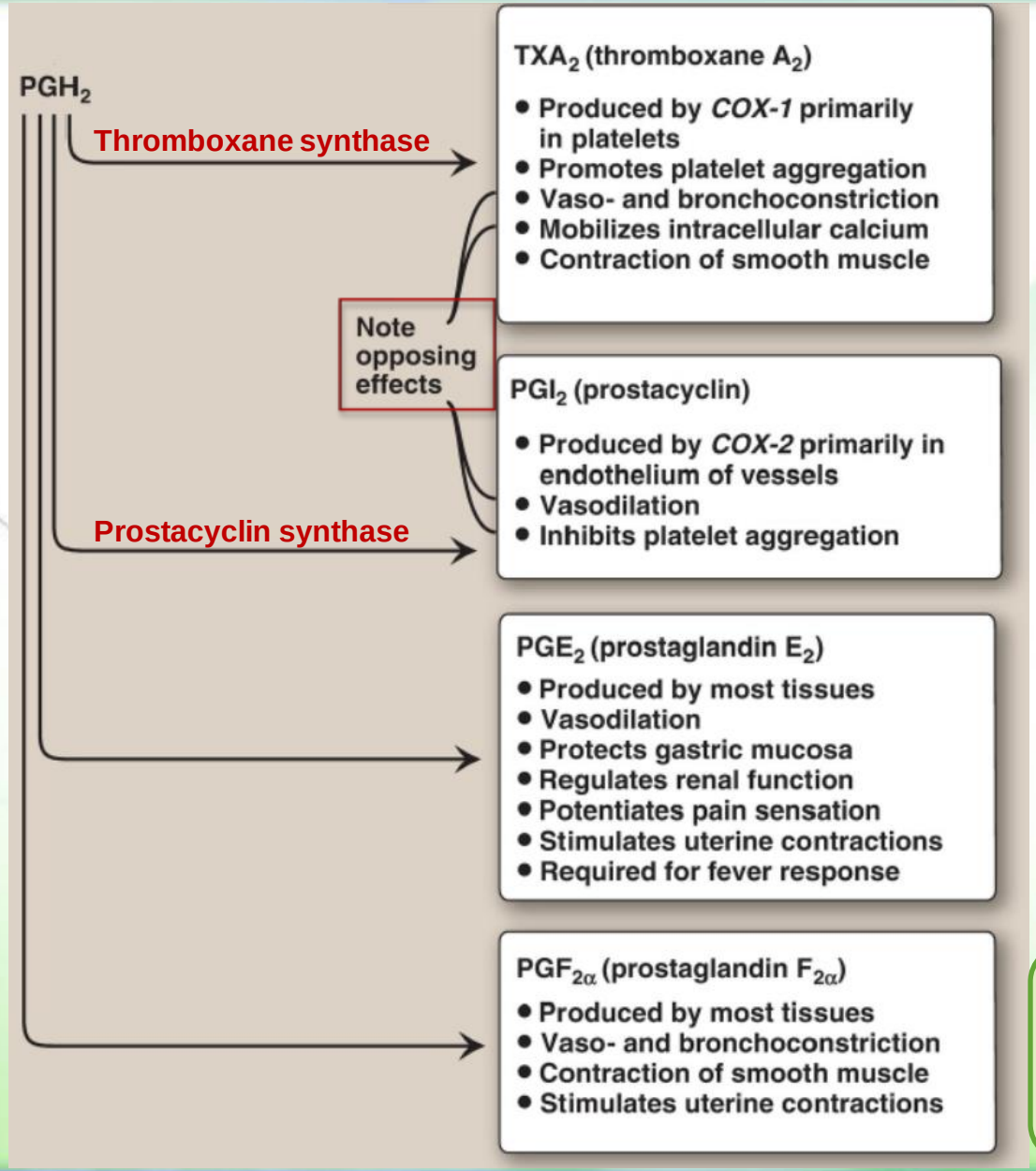


NOTE: constitutively expressed in COX1 means it is always expressed and it is not regulated

NOTE: do not pay attention to PGG2 you just need to understand that we need to convert arachidonic acid into PGH2 which requires complete enzymatic activity (two enzymatic activities, the first one is the cyclooxygenase activity and the second one is the peroxidase activity).

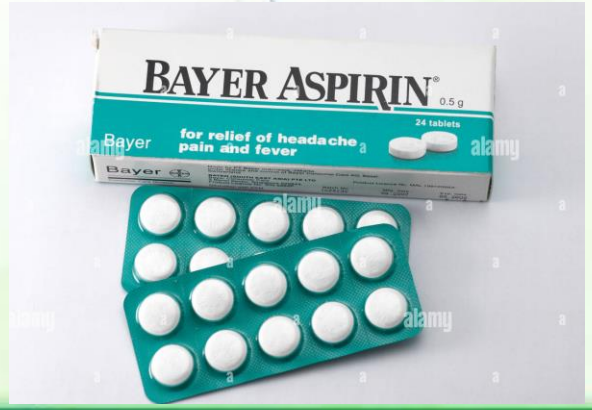
- **The complement in this slide:** COX1 is involved in functions of gastric and renal tissues so celecoxib is considered a safer drug to reduce inflammatory response without any effect on the stomach.

PGH2 is then converted to a variety of PG and TX



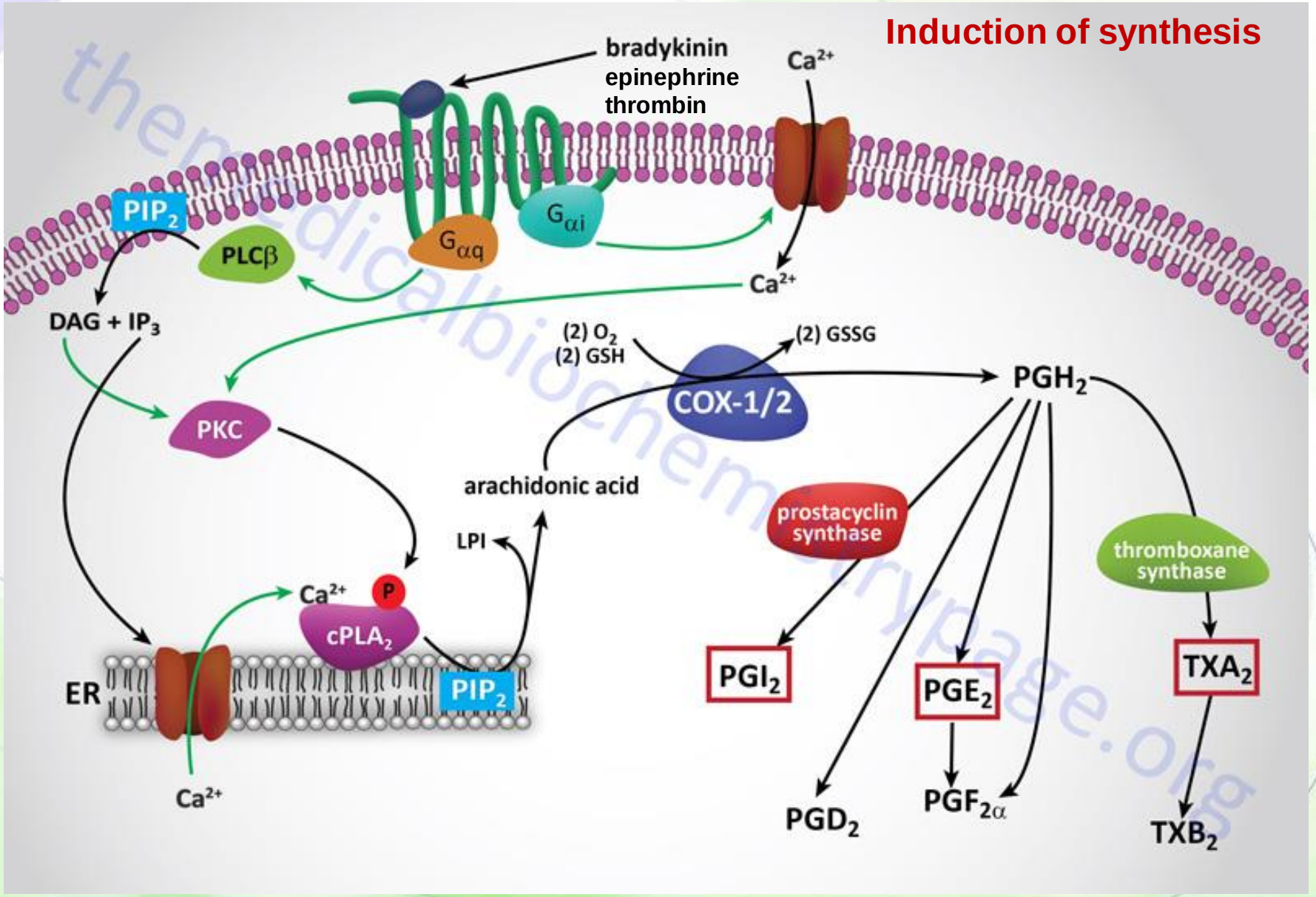
- The opposing effects of thromboxane A2 (TXA2) and prostacyclin (PGI2) limit thrombi formation to sites of vascular injury.
- Aspirin has an antithrombogenic effect. It inhibits TXA2 synthesis by COX-1 in platelets and PGI2 synthesis by COX-2 in endothelial cells
- COX-1 inhibition cannot be overcome in platelets because they cannot synthesize it anymore, but COX-2 inhibition can be overcome in endothelial cells.
- This is why low-dose aspirin is lowers the risk of stroke and heart attacks by decreasing the formation of thrombi.

NOTE: **PGH2** chooses its pathway depending on the tissue.



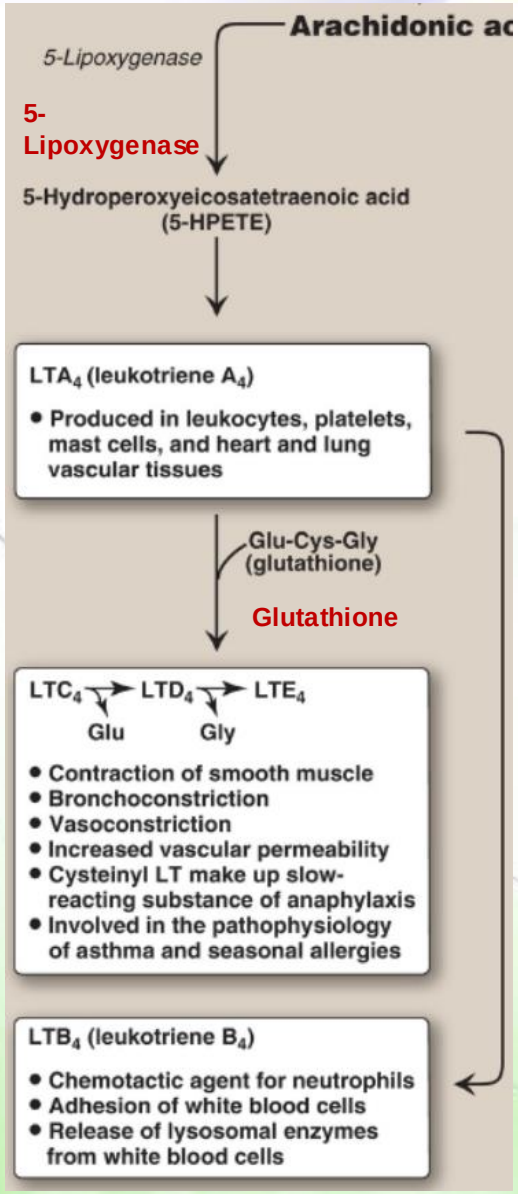
- **The complement in this slide:** platelets (where we have only COX1) don’t have a nucleus, so once aspirin inhibits synthesis of TXA2 it cannot be overcome after a period of time because once COX1 is inhibited there is no renewal of the enzyme (by transcription in the nucleus) so aspirin is considered an irreversible inhibitor in platelets
- Whereas COX-2 starts working in endothelial cells, and even if there is an inhibition by aspirin, it's okay. There is still a production of COX-2 because there is a nucleus in endothelial cells, so aspirin acts initially and inhibits COX-2, but after a long term aspirin action will diminish and we will have vasodilation again 😊

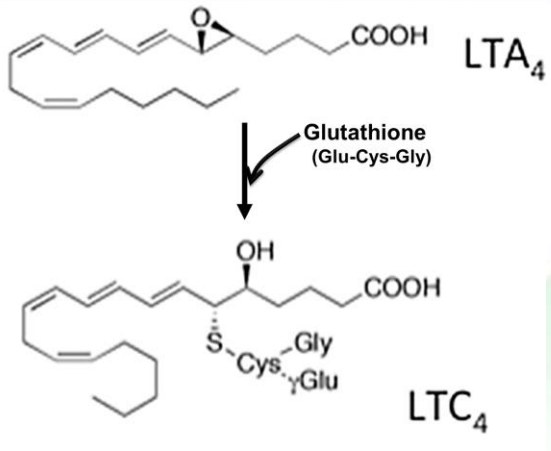
Signals leading to synthesis of eicosanoids

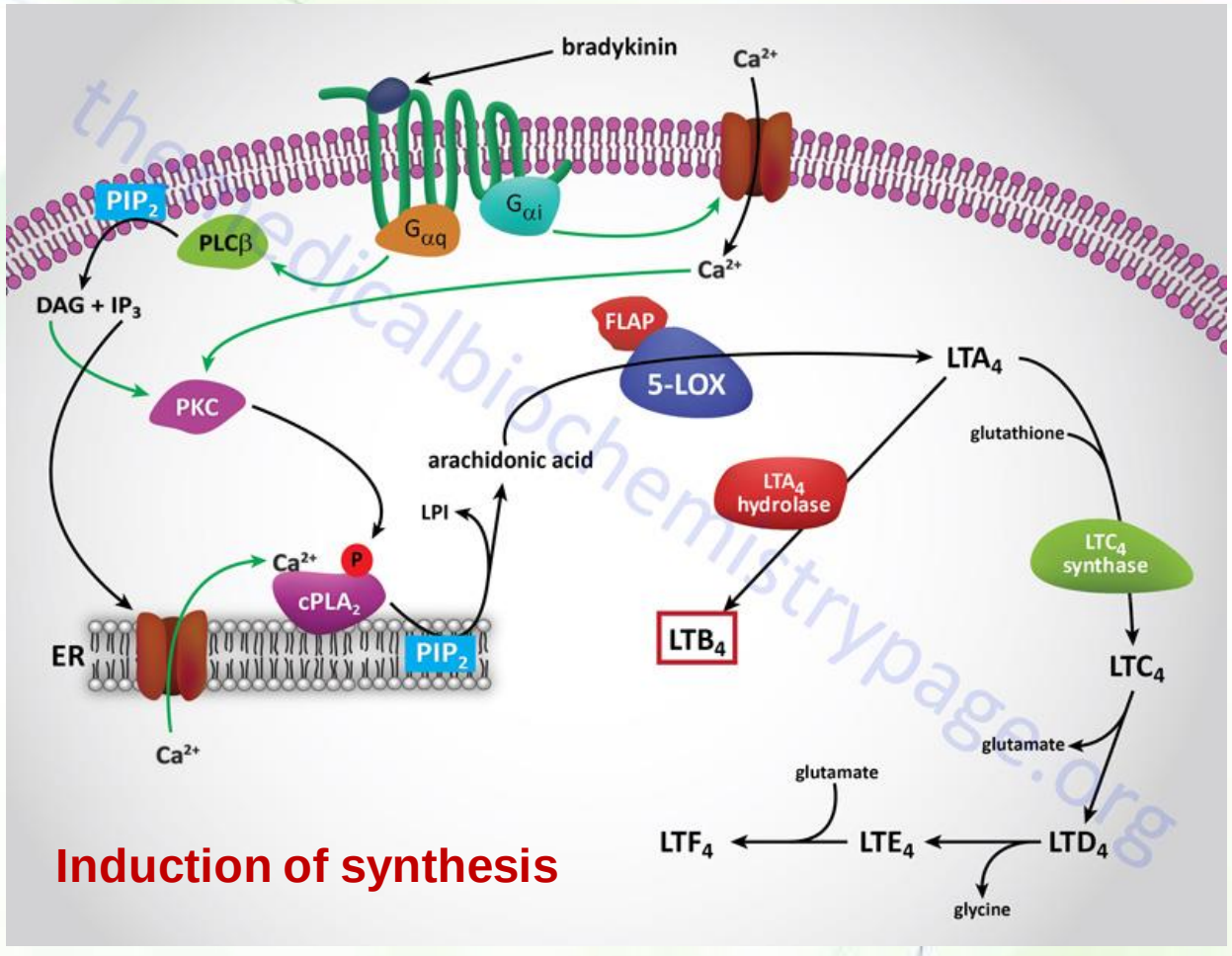


- **NOTE:** How these PGs are produced?
- Inflammatory moleculessuch as bradykinin, epinephrine and thrombin bind to a GPCR that is linked to Gαi and Gαq, Gαi open Ca+2 channels and Gαq activates PLCβ (phospholipase C β) which produce DAG and IP3 from PIP2, IP3 open Ca+2 channels in the ER, Dag simulates 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





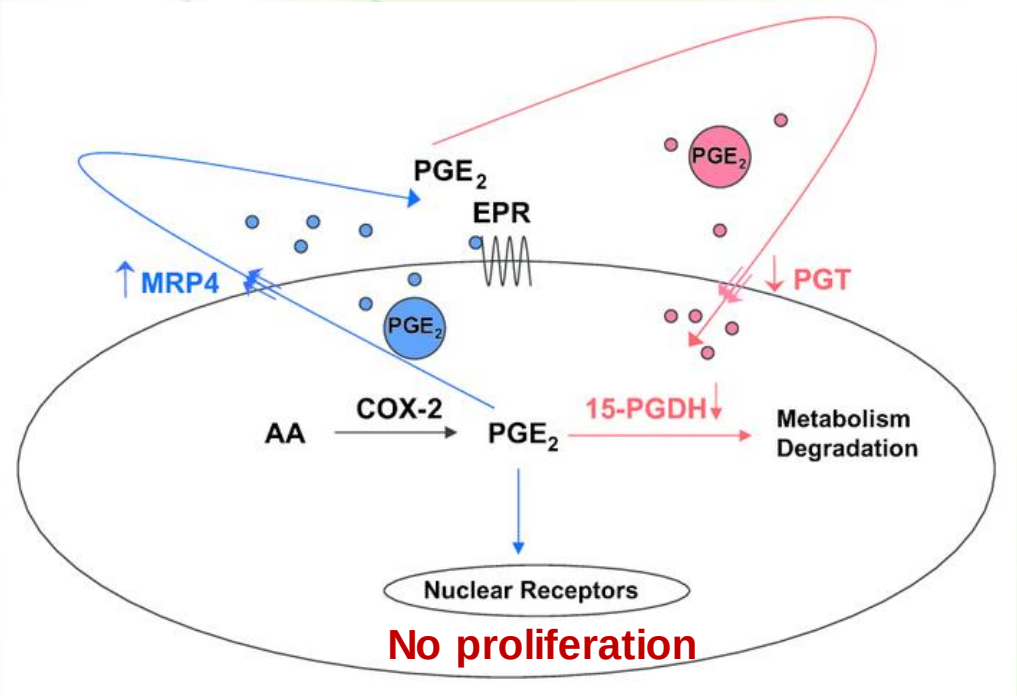


- LT are mediators of allergic response and inflammation.
- Inhibitors of 5-LOX and LT-receptor antagonists are used in the treatment of asthma.
- Note: LT synthesis is inhibited by cortisol and not by NSAID. Aspirin-exacerbated respiratory disease is a response to LT overproduction with NSAID use in ~10% of individuals with asthma.

- **NOTE:** Like the PG but instead of COX-1/2 we have 5- Lipoxygenase (5-LOX) that convert AA 5- HPETE CONVERT TO 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.
- 4- LT mediator they cause asthma
- 5-they have same action on transmembrain recetor (GPCR).

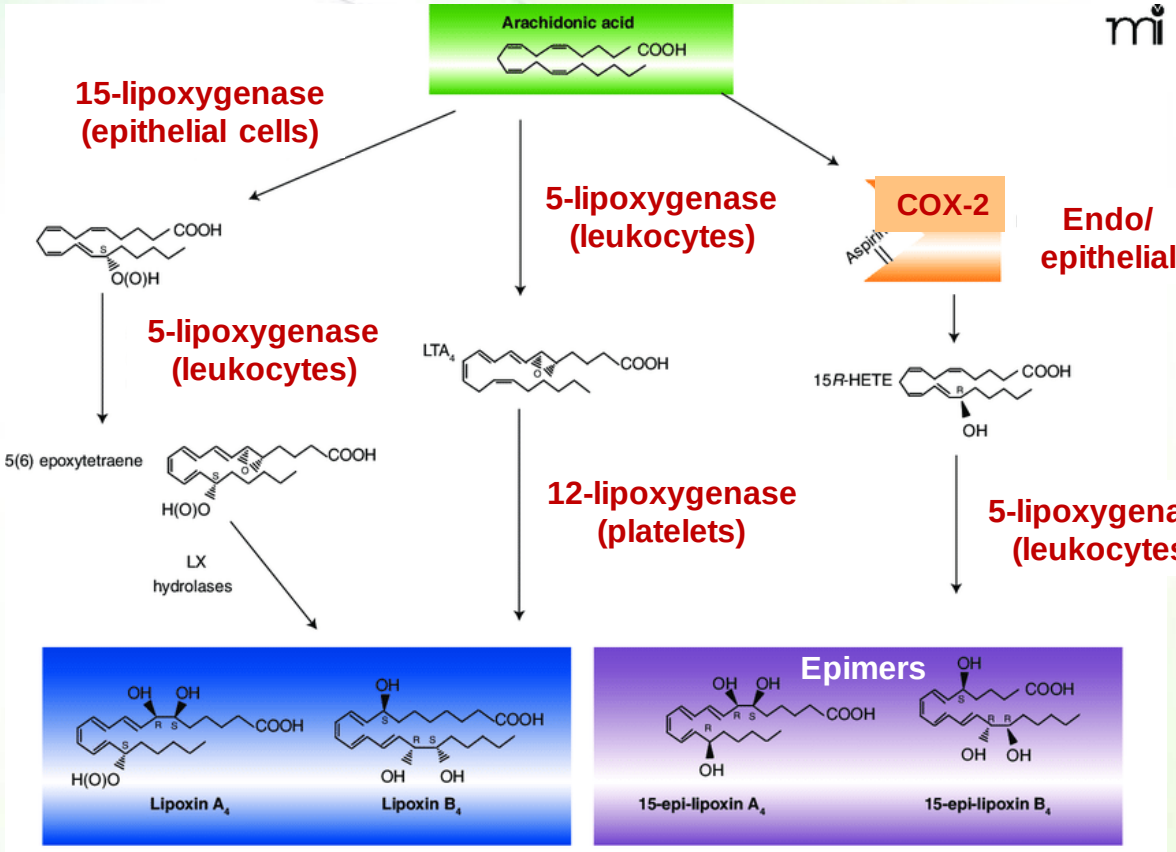
Catabolism of prostanoids

- 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.



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.
  - 15-LOX in epithelial cell, such as airway cells, followed by 5-LOX action in leukocytes.
  - Aspirin-mediated acetylation of COX-2.
    - Aspirin-induced acetylation of COX-2 alters the enzyme such that it converts arachidonic acid to biologically active LXs in monocytes and leukocytes by 5-lipoxygenase (5-LOX).



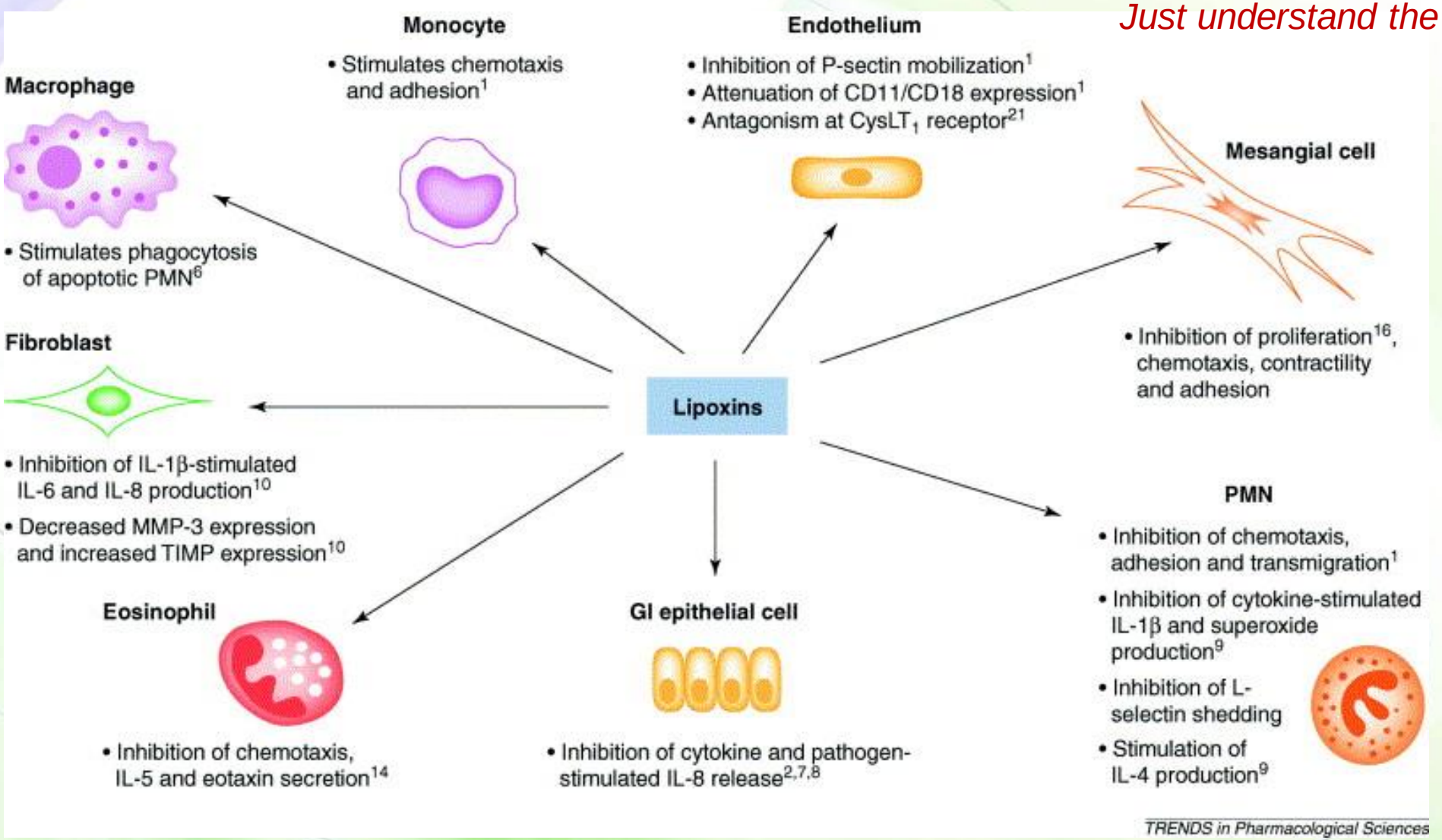
The functions of lipoxins

Do not memorize the points.
Just understand the concept

- The lipoxins LXA4 and 15 epi-LXA4 function through lipoxin A4 receptor (ALXR), a G protein-coupled receptor (GPCR) to:
  - Increase the production of prostacyclin (PGI_2) and nitric oxide (NO),
  - promote the relaxation of the vasculature,
  - inhibit polymorphonuclear leukocyte (PMN)-mediated increases in vasopermeability, and PMN chemotaxis, adhesion and migration through the endothelium,
  - stimulate phagocytosis of apoptotic PMNs by macrophages (the resolution phase of inflammatory events),
  - blocking the expression of the pro-inflammatory IL-8 by macrophages and endothelial,
  - regulate the actions of histamine leading to a reduction in edema.

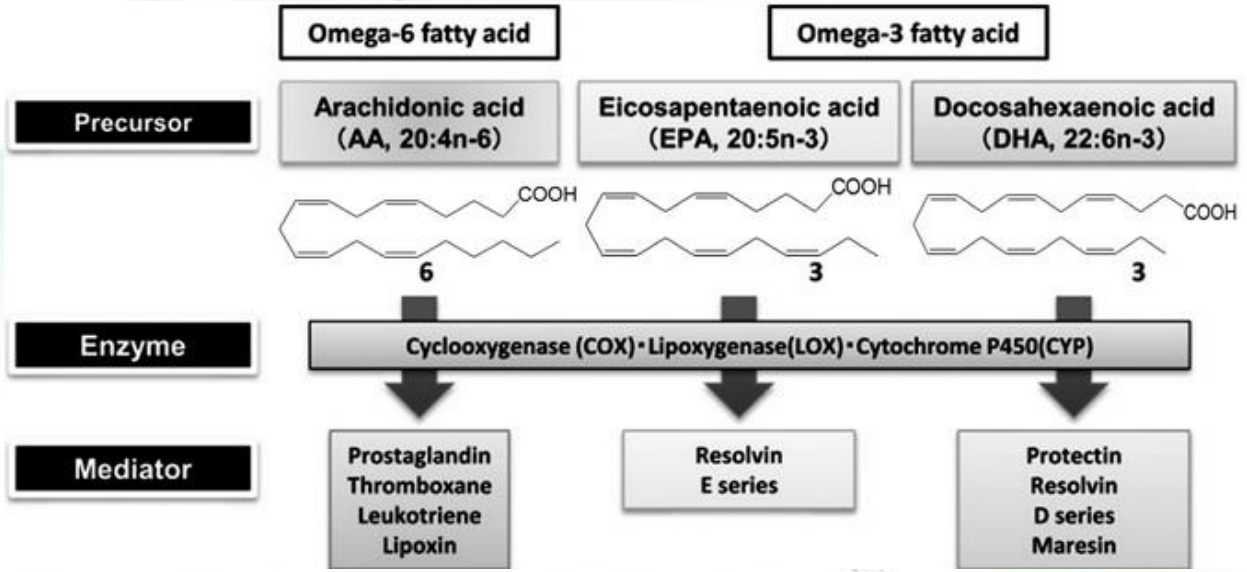
The functions of lipoxins (in picture)

Do not memorize.
Just understand the concept



The specialized pro-resolving mediators (SPM)

- Resolvins (Rv), protectins (PD), and maresins (MaR) are anti-inflammatory lipids that are derived from the omega-3 EPA- and DHA by lipoxygenases.
- Aspirin triggers their synthesis.
- They stimulate the resolution of the inflammatory responses through G protein-coupled receptors via diverse action like:
  - limiting further neutrophil recruitment to the site of inflammation
  - promoting macrophage clearance of debris, apoptotic cells and bacteria.



- Aspirin is taken daily in low dose to decrease blood clotting; it acts by inhibiting:
- A. Phosphodiesterase
- B. HMG CoA reductase
- C. Cyclooxygenase
- D. Phospholipase A2
- E. Protein kinase

- Ans:c

- The release of arachidonic acid from phosphatidylinositol is facilitated by _____

- Answer: phospholipase A2

- Aspirin effect on synthesis of lipoxins?

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