EICOSANOIDS: An Overview

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What are Eicosanoids?

Eicosanoids:

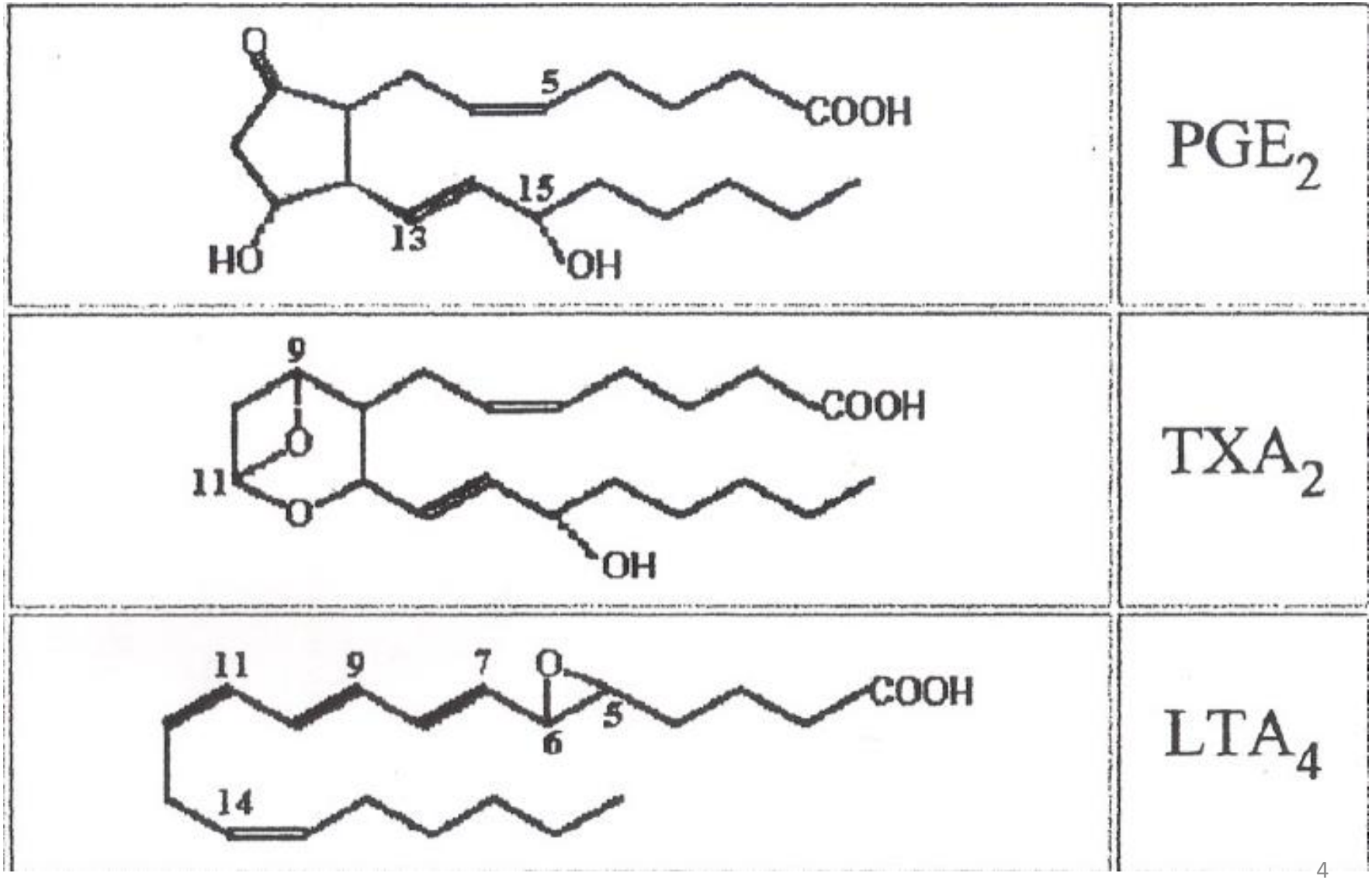
- Group of compounds containing **20 Carbon atoms**
- Derived from metabolism of **Eicosapolyenoic Fatty Acids**
  - Polyunsaturated fatty acids with 20 carbon atoms,
- Eicosanoids are Paracrine "Local hormones" (**Why?**)
  - Because of their specific effects on target cells very close to their site of synthesis,
  - They are rapidly degraded, thus are not transported to distal sites for action;

What are the Clinically Relevant Eicosanoids?

Clinically Relevant Eicosanoids are (**Fig. 1**):

- **Prostaglandins (PGs)**:
  - Originally assumed to be produced in Prostate gland, but are produced in Seminal vesicles and many other tissues;
- **Thromboxanes (TXs)**:
  - Originally assumed to be produced in Platelets (Thrombocytes)
- **Leukotrienes (LTs)**:
  - Originally assumed to be produced in Leukocytes,
- **Prostacyclins (PGIs),**
- **Lipoxins (LXs),**
- **PGs, TXs and PGIs are collectively known as Prostanoids**

Fig. 1: Schematic diagrams of the structures of some Clinically relevant Eicosanoids



http://web.indstate.edu/thcme/mwking/lipid-synthesis.h

What are the precursors for biosynthesis of Eicosanoids?

- Principle Eicosanoids are from **Arachidonic acid**
  - (cis-5, 8, 11, 14 – Eicosatetraenoic acid; **)**
- Arachidonic acid is **ω6** Polyunsaturated fatty acid; **(ω6, 20:4);**

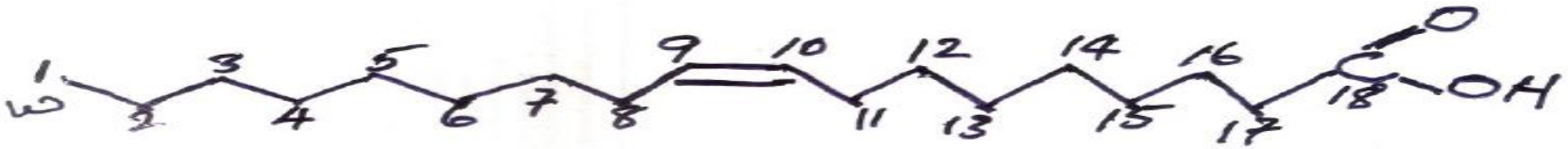
- Minor Eicosanoids are from **Dihomo-γ-Linoleic acid** and **Eicosapentaenoic acid (EPA, ω3, 20:5);**

How important are the Essential Fatty Acids?

- Dietary Essential Fatty Acids are **Omega** Fatty Acids:
  - **Linoleic Acid (ω-6, 18:2) ,**
  - **α-Linolenic Acid (ω-3, 18:3)**
  - **Arachidonic Acid is semi-essential fatty acid**
    - it can be produced from Linoleic acid;
- **Arachidonic Acid:** precursor for clinically relevant Eicosanoids;
- **Linoleic acid:** precursor for Dihomo-γ-Linoleic acid and Eicosapentaenoic acid;
- Dietary deficiency of **Linoleic acid** seriously threaten the ability of the body to synthesize Eicosanoids,

What do you understand by "Omega" Fatty Acids?

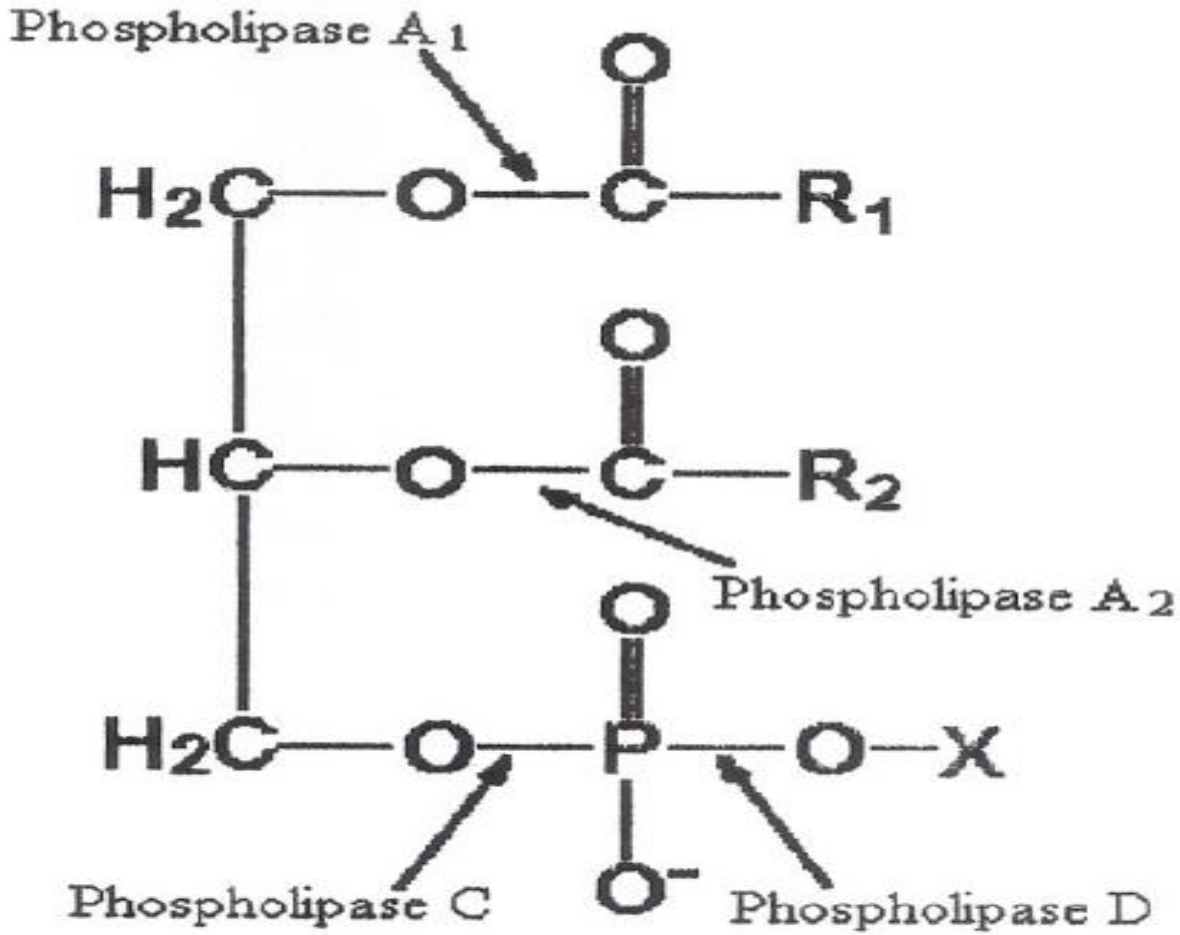
Fig. 2: OMEGA NOMENCLATURE OF FATTY ACIDS



What are the sources of Arachidonic acid?

- Major source of Arachidonic acid is cellular stores, predominantly located at **C-2** position of membrane Phospholipids (Phosphatidyl-Inositol & Phosphatidyl-Choline),
- **Phospholipase A_2** catalyzes hydrolysis of membrane Phospholipids to produce Arachidonic acid as one of its products (**Fig. 3**),
- Dietary source of Arachidonic acid is Linoleic acid;

Fig. 3: Sites of action of Phospholipases on Phospholipid



Sites of action of the phospholipases A_1, A_2, C and D.

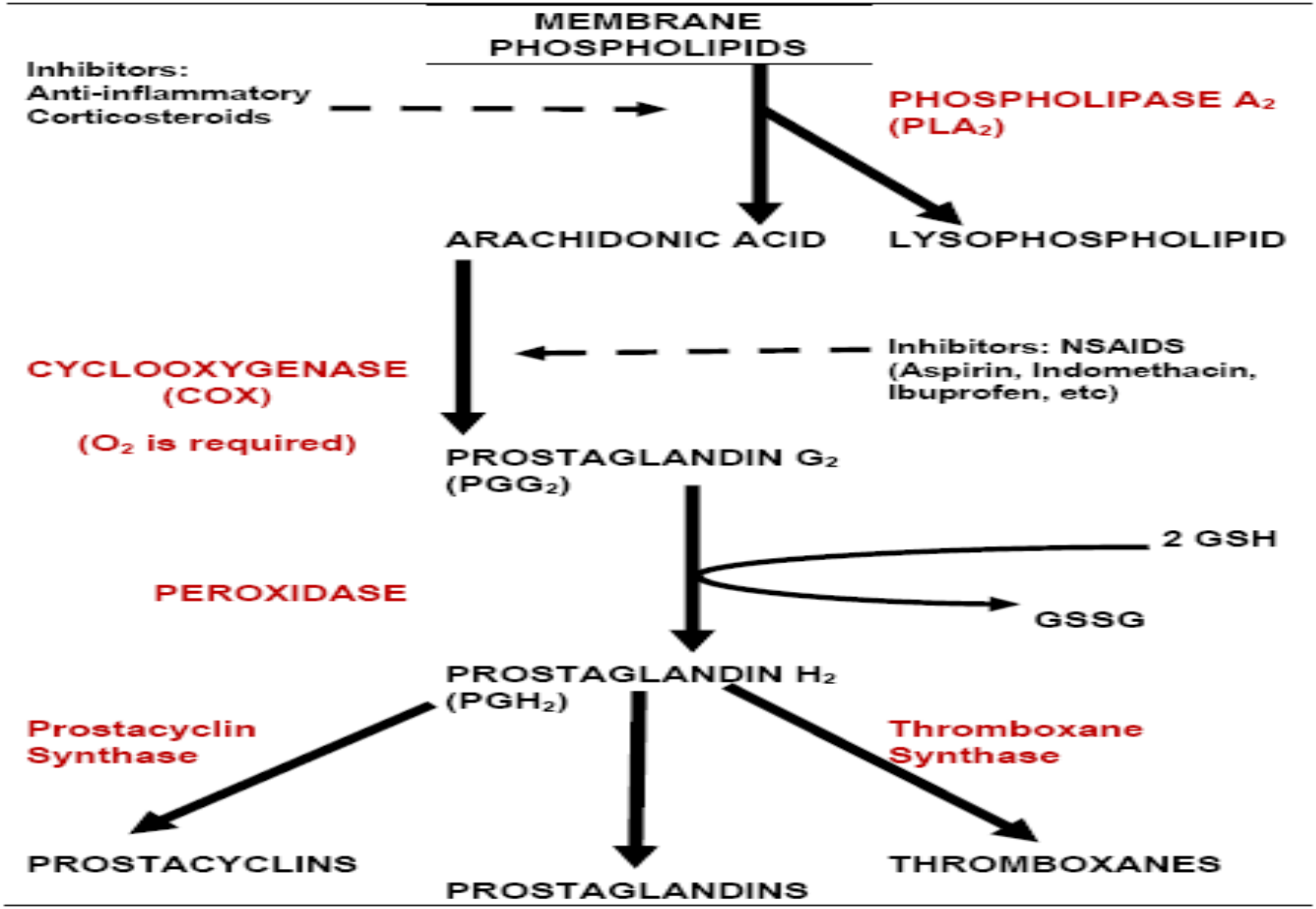
http://web.indstate.edu/thcme/mwking/lipid-synthesis.html

Cyclic pathway for biosynthesis of PGs and TXs

- All mammalian cells except the Red Blood Cells can synthesize Eicosanoids,
- **Fig. 4:** Summary of **Cyclic Pathway** for biosynthesis of clinically relevant **Prostaglandins** and **Thromboxanes** from **Arachidonic acid**,
- **Bradykinin, Epinephrine or Thrombin can activate Phospholipase A_2 (PLA_2),**
- **PLA_2** hydrolyzes Phospholipids in cell membrane to produce **Arachidonic acid**, which is the **Substrate** for **Cyclic Pathway**,

- Cyclic Pathway is catalyzed by **Prostaglandin Endo-peroxide Synthase** –made up of 2 enzymes:
  - **Cyclooxygenase,**
  - **Peroxidase**
- Prostaglandin Endo-peroxide Synthase is called **Cyclooxygenase (COX);**
- Nitric Oxide (NO) can initiate the biosynthesis of Prostaglandin
- Inhibitors of Nitric Oxide Synthase Inhibits synthesis of Prostaglandins;

Fig. 4: Cyclic Pathway for biosynthesis of Prostaglandins, Prostacyclins and Thromboxanes



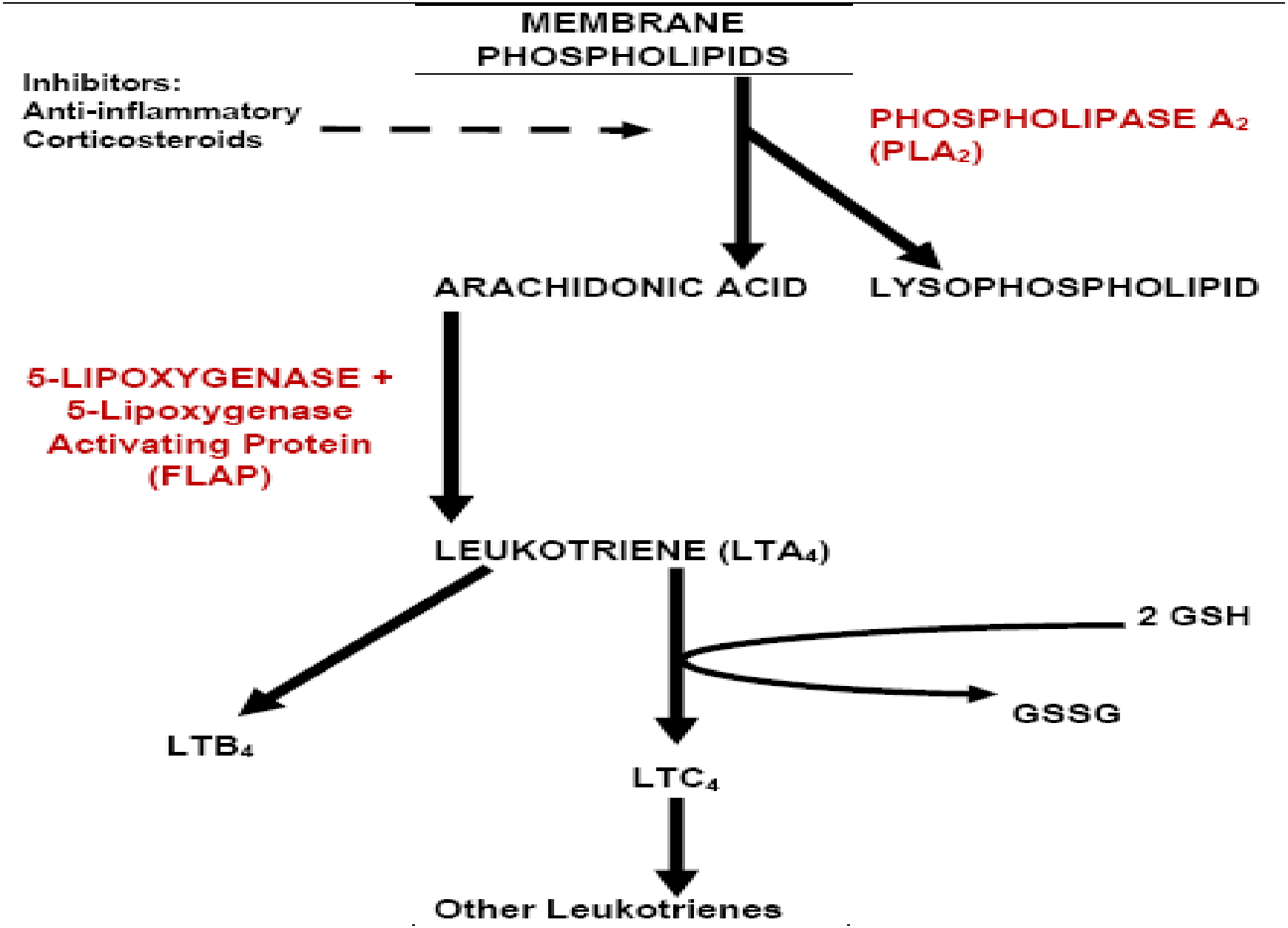
Why is Cyclooxygenase (COX) called "Suicide Enzyme"?

- **COX:** is the major enzyme in the Cyclic Pathway;
- COX can "**Switch off**" biosynthesis of Prostaglandins by self-catalyzed destruction (**Enzyme Suicide**),
- Self destruction may be due to presence in mammalian tissues of a specific enzyme: **15-Hydroxy-Prostaglandin Dehydrogenase** (**15 HPD**),
- Blocking the action of **15 HPD** (with Sulfa-Salazine or Indomethacin) prolong the half-life of Prostaglandins,

Linear pathway for biosynthesis of Leukotrienes

- **Fig 5: Linear Pathway** for biosynthesis of **Leukotrienes;**
- **Bradykinin activates Phospholipase A_2 (PLA_2),**
- **PLA_2** hydrolyzes Phospholipids in membrane to produce **Arachidonic acid**, the **Substrate** for **Linear Pathway**,
- **5-Lipoxygenase** is activated by membrane protein **FLAP** (**5-Lipoxygenase-Activating Protein**);
  - **FLAP** binds Arachidonic acid, facilitating its interaction with 5-Lipoxygenase;
- **5-Lipoxygenase, FLAP,** and **Phospholipase A_2 form a complex** in association with the nuclear envelope during biosynthesis of Leukotrienes in Leukocytes;

Fig. 5: Linear pathway for biosynthesis of some Leukotrienes



How do Eicosanoids interact with receptors in target cells?

- Prostaglandins and other Eicosanoids acts via **Receptor-Mediated G-proteins** Linked to signaling pathways (**Metabotropic Receptors or 2nd Messenger system**)
- Depending on the cell type, activated **G-protein** may:
  - Stimulate formation of Cyclic-AMP,
  - Inhibit formation of Cyclic-AMP,
  - Activate a Phosphatidyl-Inositol Signal pathway leading to Intracellular Ca^{++} release,
- Some Prostaglandin receptors are related to a family of Nuclear receptors with Transcription Factor activity;

State some general functions of Eicosanoids

- Prostaglandins have wide range of functions:
- **Prostaglandins**:
  - Cause pain, Inflammation and Fever,
  - Cause contraction of smooth muscle,
  - Involved in Reproductive functions, including Induction of Labor,
  - Involved in Blood Pressure Control,
  - Suppress acid secretion in the stomach, etc
- **Thromboxanes** affect Platelet aggregation and blood clotting,

State some specific functions of Prostaglandins

- Prostaglandins (PGE_2 and PGE_1) can induce:
  - Signs of inflammation, redness and Heat (due to Arteriolar Vasodilatation),
  - Swelling and Edema resulting from increasing capillary permeability,
    - These condition can be treated with Corticosteroids that Inhibit biosynthesis of Prostaglandins,
- Bradykinin and Histamine can activate biosynthesis of PGE_2 in region of Hypothalamus where body temperature is regulated, thus resulting in increase body temperature causing fever (Pyrogenic effect of Prostaglandins)

- Interleukin-1 (IL-1α) can act on the Hypothalamus causing increase in biosynthesis of Prostaglandins, thereby increasing body temperature,
  - Prostaglandins are “Pyrogenic” because they can raise body temperature,
- Aspirin (Anti-pyretic), inhibits Pyrogenic effect of PGs;
- Prostaglandins (PGE, PGA) and Prostacyclin (PGI_2), are Vasodilators,
  - They lower systemic arterial pressure, thereby increasing local blood flow and decreasing peripheral resistance,

What are the sites of action of inhibitors of Prostaglandin biosynthesis?

- Two types of Therapeutically useful drugs affect biosynthesis of Prostaglandins,
- **First**: Non-steroidal Anti-Inflammatory drug (**NSAIDs**):
  - Aspirin (Acetylsalicylic acid)
  - Indomethacin
  - Phenylbutazone
- These drugs block biosynthesis of Prostaglandin by irreversibly inhibiting **Cyclooxygenase (COX)** (**Fig: 4**)
- Aspirin, inhibition occurs by Acetylation of COX,

- **Second:** Steroidal Anti-inflammatory Drug Corticosteroid
- Corticosteroid block biosynthesis of Prostaglandin by inhibiting the action of Phospholipase A_2,
  - It tends to interfere with mobilization of Arachidonic acid, which is the substrate for COX (**Fig. 4**),

- Factors that control biosynthesis of Prostaglandins are poorly understood, but, in general, Prostaglandin release seems to be triggered following Hormonal or Neural excitation or after muscular activity,
- Examples:
  - Histamine stimulates increase in Prostaglandin concentration in Gastric Perfusates,
  - Prostaglandins are released during labor and after cellular injury,

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