SOME CLINCALLY RELEVANT EICOSANOIDS: An Overview

UNIVERSITY OF PNG
SCHOOL OF MEDICINE AND HEALTH SCIENCES
DIVISION OF BASIC MEDICAL SCIENCES
DISCIPLINE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY
M. Med Part I

VJ Temple

What are Eicosanoids?

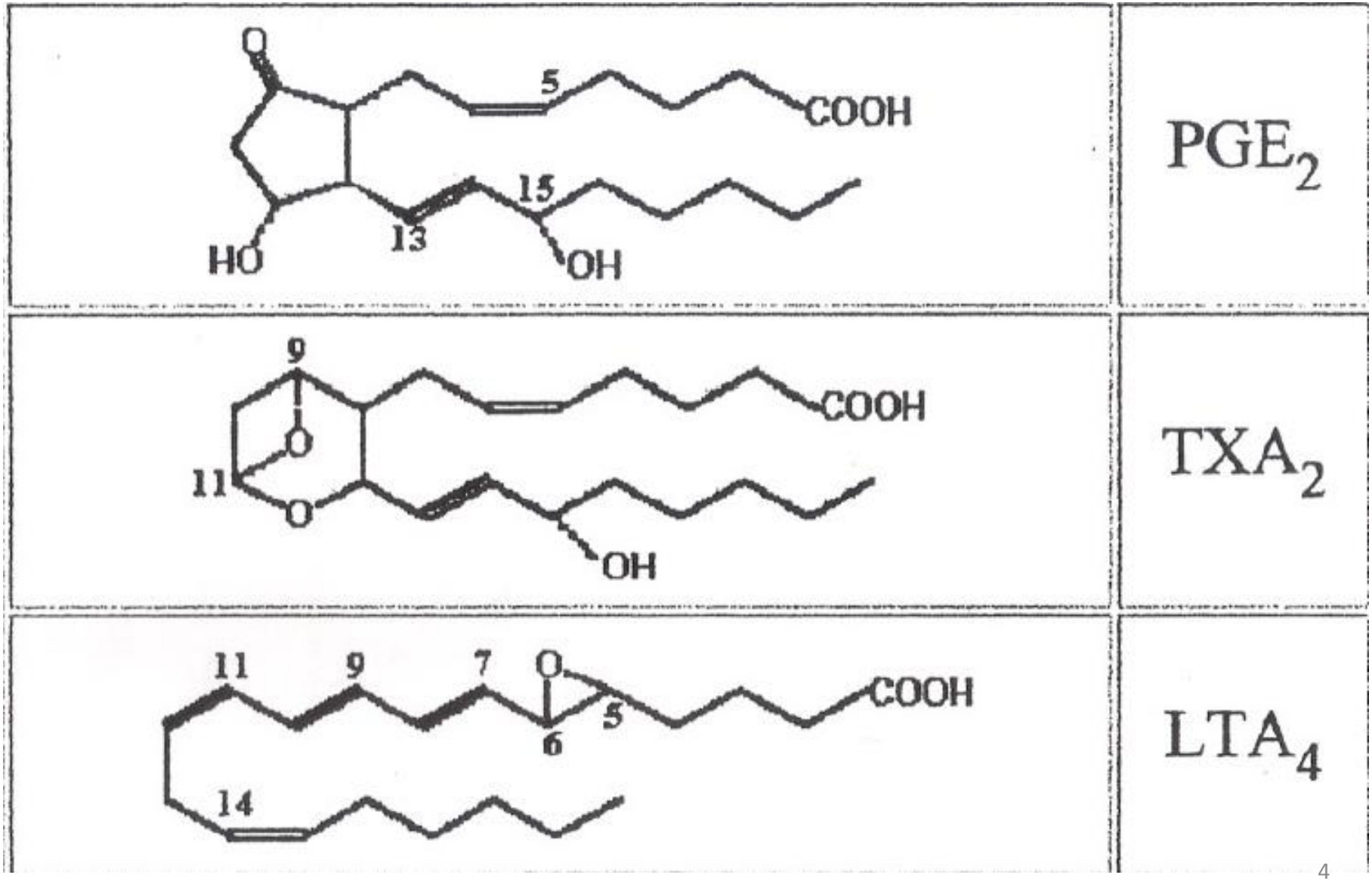
EICOSANOIDS:

- Group of compounds containing **20 Carbon atoms;**
- Derived from metabolism of **Eicosapolyenoic Fatty Acids**
  - Polyunsaturated fatty acids with 20 Carbons,
- Eicosanoids are **Paracrine** "Local hormones" (**Why?**)
  - They have specific effects on target cells very close to their site of biosynthesis,
    - They are rapidly degraded, thus cannot be transported to distal sites for action;
    - Examples: Growth factors, clotting factors

What are the Clinically Relevant Eicosanoids? (Fig. 1)

- **Prostaglandins (PGs)**:
  - Assumed to be produced in Prostate gland, but are produced in Seminal vesicles and many other tissues;
- **Thromboxanes (TXs)**:
  - Assumed to be produced in Platelets (Thrombocytes);
- **Leukotrienes (LTs)**:
  - Assumed to be produced in Leukocytes,
- **Prostacyclins (PGIs),**
- **Lipoxins (LXs),**
- **PGs, TXs and PGIs are called 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**
  - Arachidonic acid is **ω6** Polyunsaturated fatty acid; **(ω6, 20:4);**

- **Minor Eicosanoids** are from:
  - **Dihomo-γ-Linoleic acid (ω6),**
  - **Eicosapentaenoic acid (EPA, ω3, 20:5);**

- **Linoleic acid:** precursor for Eicosapentaenoic acid and Dihomo-γ-Linoleic acid;

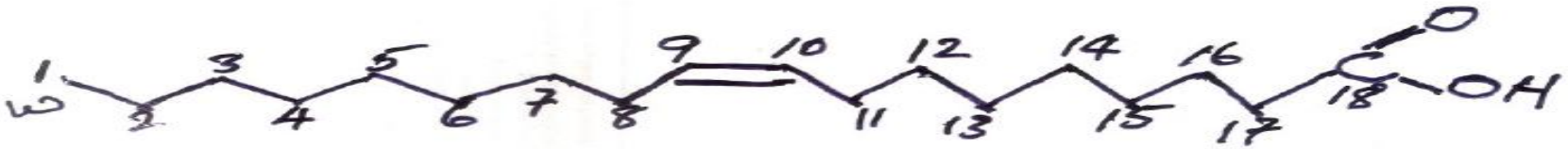
What are the Essential Fatty Acids and why are they important?

- Dietary Essential Fatty Acids are **Omega** Fatty Acids:
  - **α-LINOLENIC ACID (ω-3, 18:3),**
  - **LINOLEIC ACID (ω-6, 18:2),**
  - **ARACHIDONIC ACID is semi-essential fatty acid;**
    - Because it can be synthesize from **Linoleic acid**;

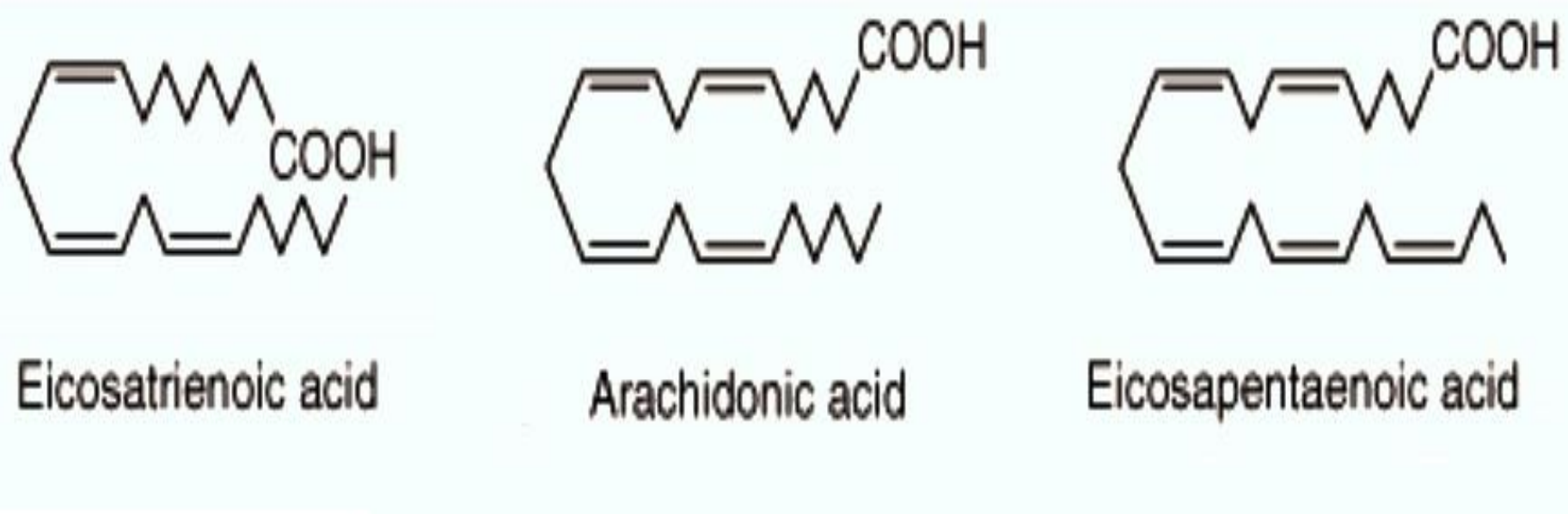
- Dietary deficiency of **LINOLEIC ACID** compromises ability of the body to synthesize **Eicosanoids**,

What do you understand by "Omega" Fatty Acids?

Fig. 2: OMEGA NOMENCLATURE OF FATTY ACIDS



Examples of Omega fatty acids



- Eicosatrienoic acid (γ-Linolenic acid, ω6)
- **Arachidonic acid (ω6)**
- **Eicosapentaenoic acid (ω3)**

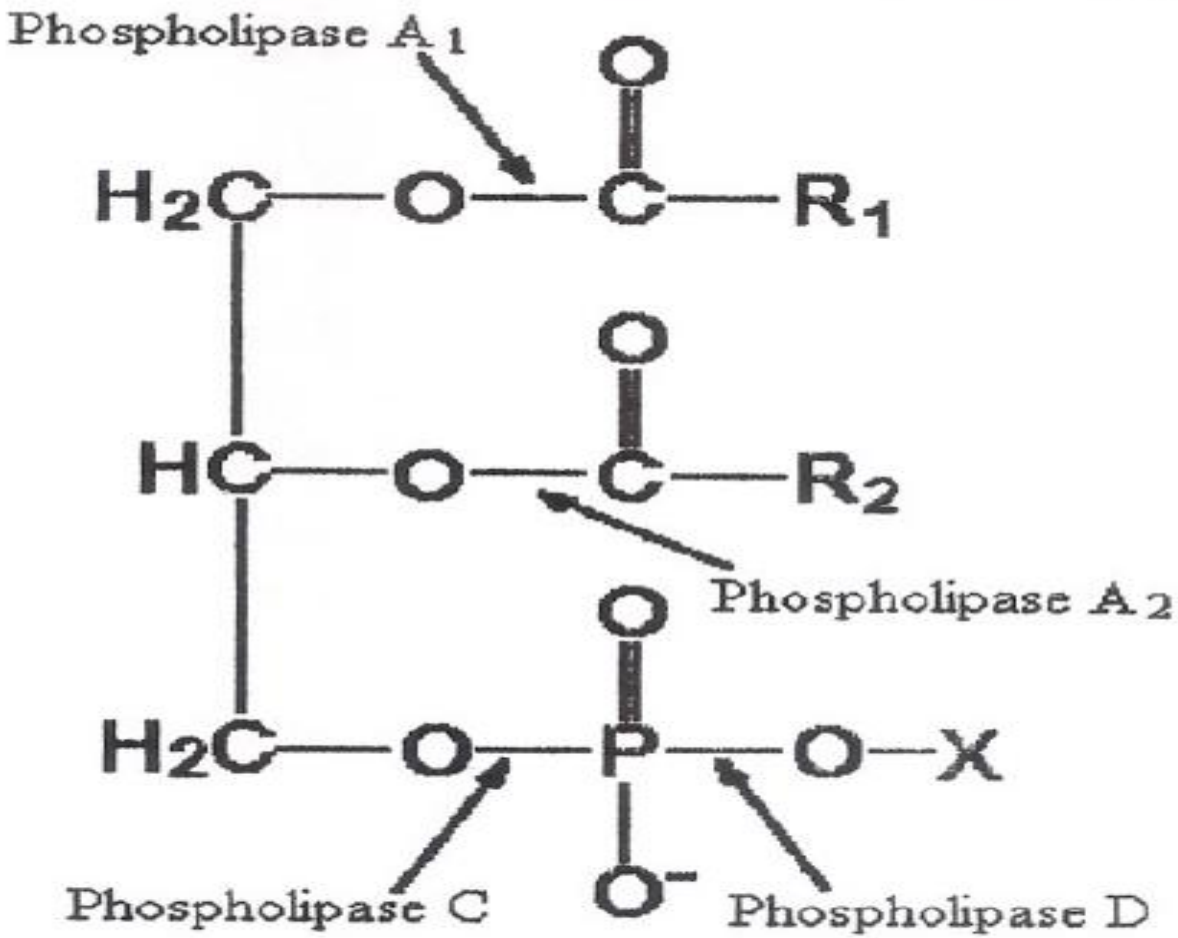
Dietary balance of the Omega fatty acids

- **ω6 and ω3** are not inter-convertible in humans,
- Diets rich in ω3 fatty acids result in high content in membrane phospholipids,
  - Recommended ratio: 1-4: 1 (ω6 : ω3)
  - Typical western diet: 14-25: 1 (ω6 : ω3)
- Individuals consuming diet rich in ω-6 FAs may shifts their physiological state to one that is pro-inflammatory, pro-thrombotic and proaggregatory which may lead to heart disease in susceptible individuals;

What are the major sources of Arachidonic acid?

- **Major source** is cellular stores,
  - It is predominantly located at **C-2** position of membrane Phospholipids:
    - **Phosphatidyl-Inositol,**
    - **Phosphatidyl-Choline (Lecithin)**
      - **Phospholipase A_2 (PLA_2)** catalyzes hydrolysis of membrane Phospholipids to produce Arachidonic acid (**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

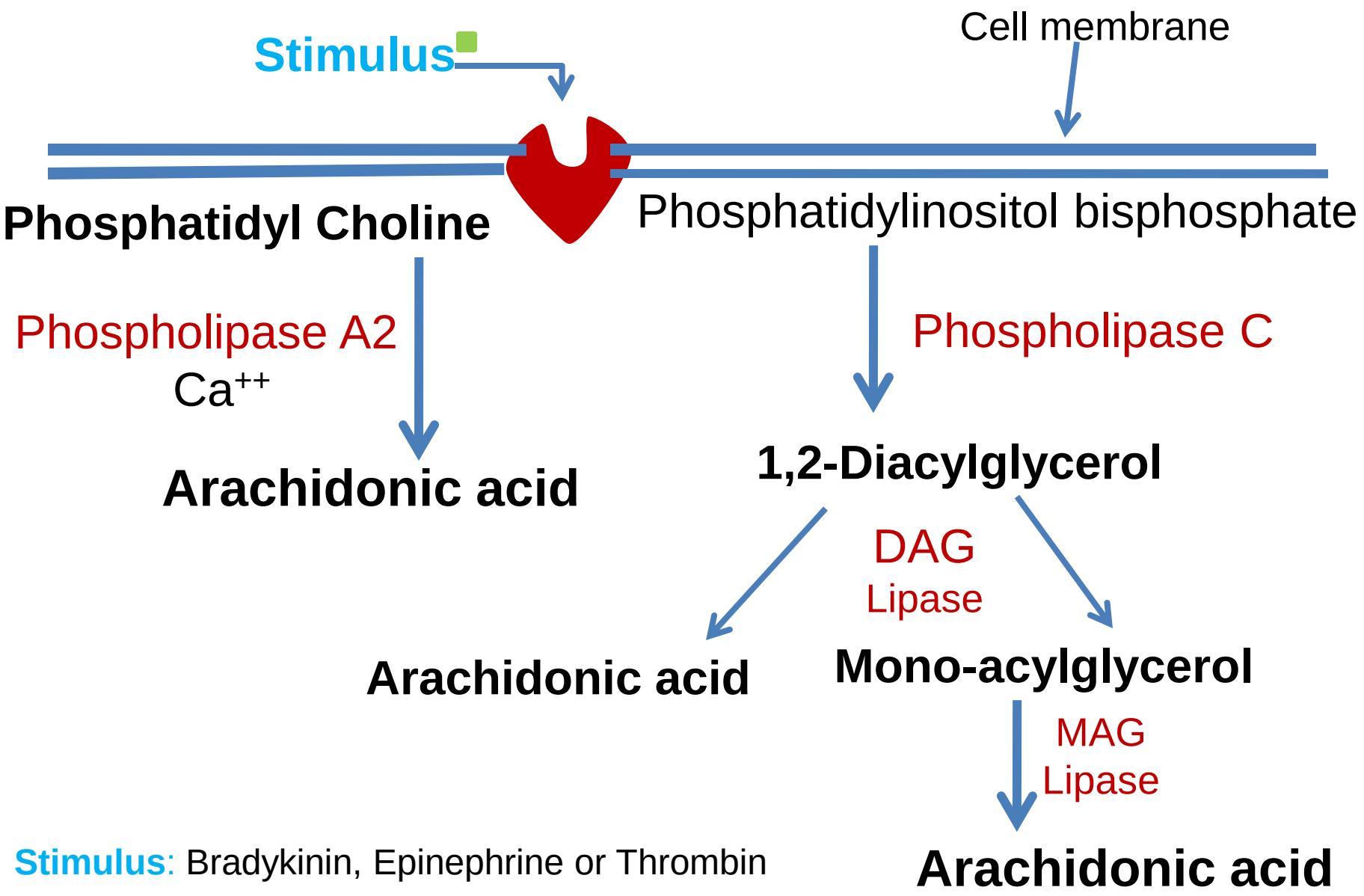
Dietary **Linoleic Acid** (C18:2, ω6) (plant oils)

Elongase

Desaturase

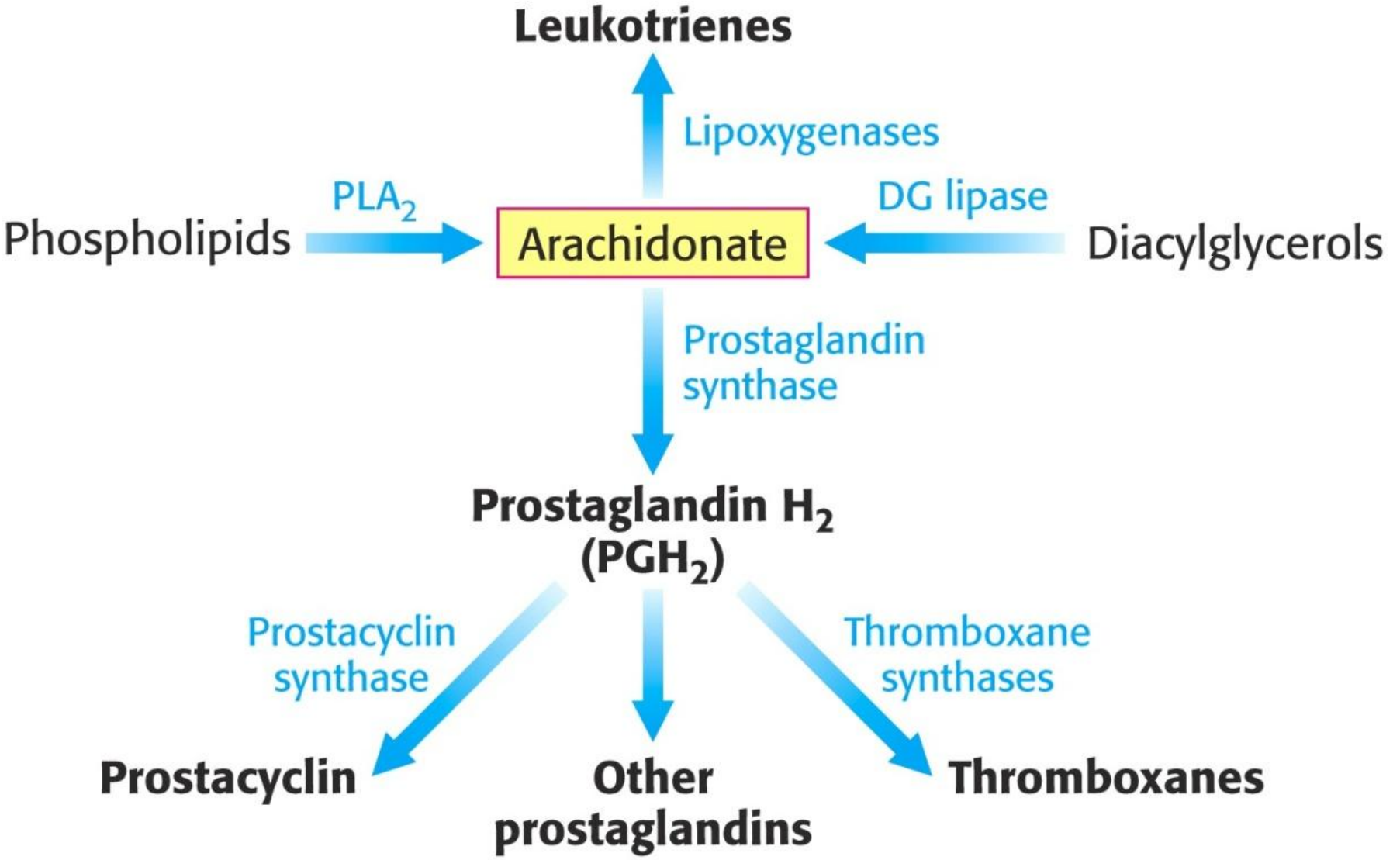
Arachidonic Acid (C20: 4, ω6)

How is Arachidonic acid release from membrane lipids



Stimulus: Bradykinin, Epinephrine or Thrombin

General pathways for biosynthesis of Eicosanoids



CYCLIC PATHWAY for biosynthesis of PGs and TXs

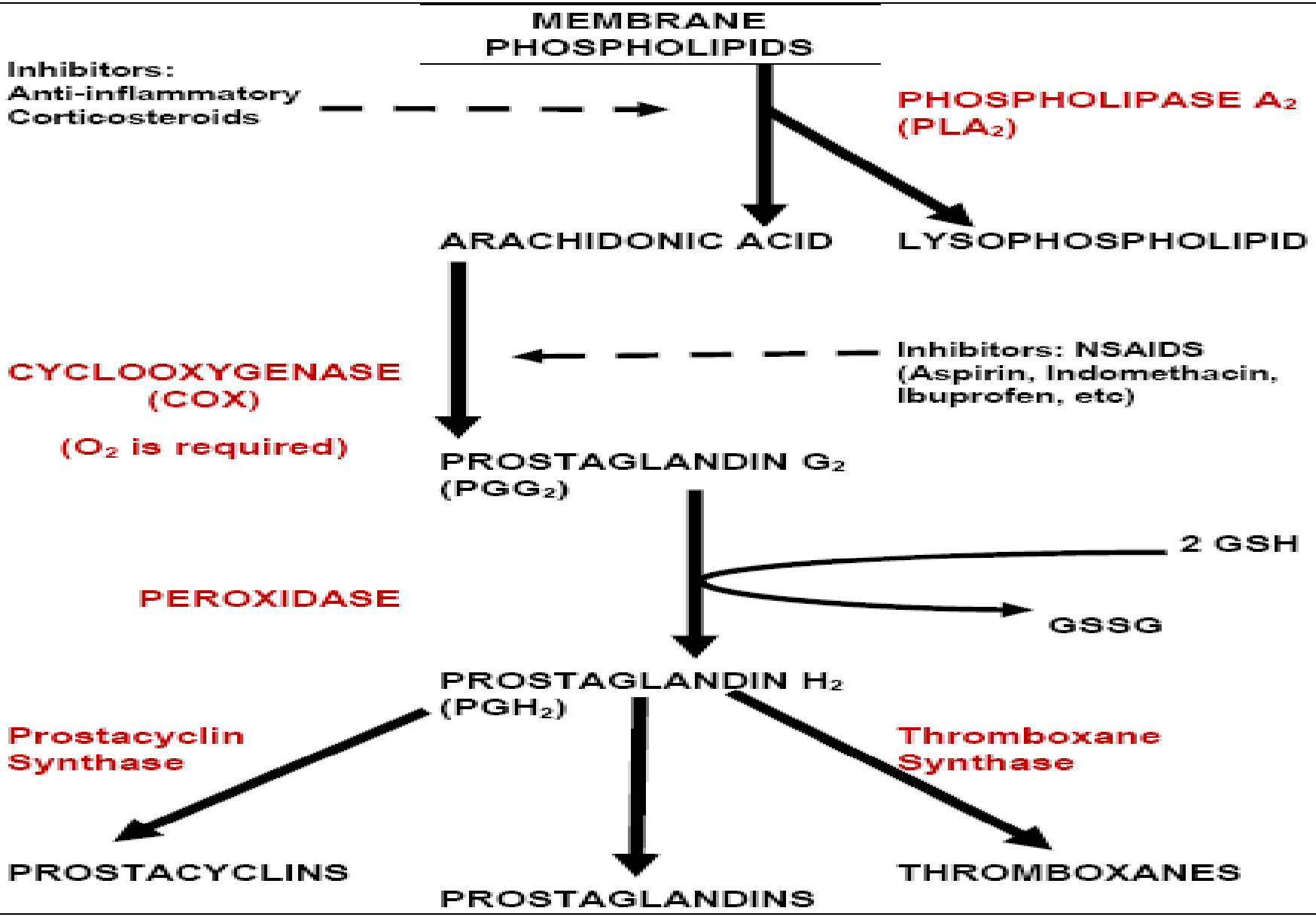
- **Eicosanoids are produced in all cells except RBC**,
  - **Fig. 4: Cyclic Pathway** for **biosynthesis of Prostaglandins** & **Thromboxanes;**
- **Bradykinin, Epinephrine or Thrombin activate Phospholipase A_2 (PLA_2),**

- **PLA_2** hydrolyzes Phospholipids in cell membrane to produce **Arachidonic acid**, which is **Substrate** for the **Cyclic Pathway**,

- Major enzymes in Cyclic Pathway:
  - **PROSTAGLANDIN ENDO-PEROXIDE SYNTHASE** made up of 2 enzymes:
    - **CYCLOOXYGENASE (COX),**
    - **PEROXIDASE;**

- IMPORTANT TO NOTE:
  - **Nitric Oxide** (NO) **initiates** the biosynthesis of Prostaglandins,
  - **Inhibitors** of **Nitric Oxide Synthase** can **inhibit** biosynthesis of Prostaglandins;

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



Why is Cyclooxygenase (COX) called “Suicide Enzyme”?

- **COX** can “**Switch off**” Prostaglandin biosynthesis by self-catalyzed destruction (**Enzyme Suicide**),
- Self destruction may be due to presence in tissues of specific enzyme: **15-Hydroxy-Prostaglandin Dehydrogenase** (**15 HPD**),

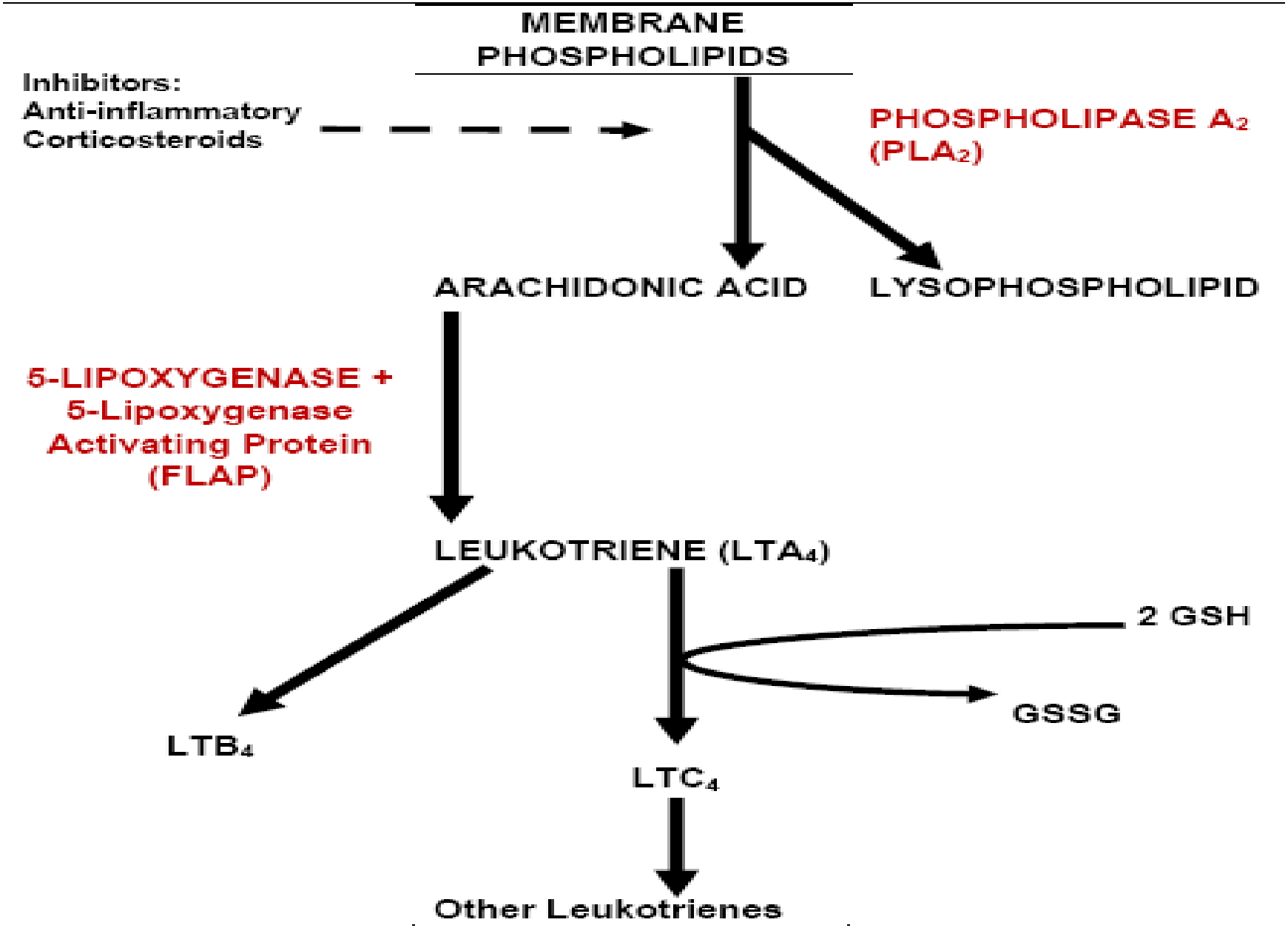
- Blocking the action of **15 HPD** (with **Sulfa-Salazine** or **Indomethacin**) can prolong the half-life of Prostaglandins,

Linear pathway for biosynthesis of Leukotrienes (Fig. 5)

- **PLA_2** hydrolyzes Phospholipids to produce **Arachidonic acid**, 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**;

Fig. 5: Linear pathway for biosynthesis of some Leukotrienes



How do Eicosanoids interact with receptors in target cells?

- Eicosanoids acts via **Receptor-Mediated G-proteins** Linked to signaling pathways,
  - **Metabotropic Receptors or 2nd Messenger system**
- Depending on cell type, activated **G-protein** may:
  - **Stimulate formation of Cyclic-AMP,**
  - **Inhibit formation of Cyclic-AMP,**
  - **Activate Phosphatidyl-Inositol Signal pathway leading to Intracellular Ca^{++} release,**

Some general functions of Eicosanoids:

- Induction of inflammation,
- Mediation of pain signals,
- Induction of fever,
- Smooth muscle contraction (including uterus),
- Smooth muscle relaxation,
- Protection of stomach lining,
- Simulation of platelet aggregation,
- Inhibition of platelet aggregation,
- Sodium and water retention,

State some general functions of Eicosanoids

- **Prostaglandins** have wide range of functions:
  - Cause pain, Inflammation and Fever,
  - Cause contraction of smooth muscle,
  - Involved in Reproductive functions,
  - Involved in Blood Pressure Control,
  - Suppress acid secretion in 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,

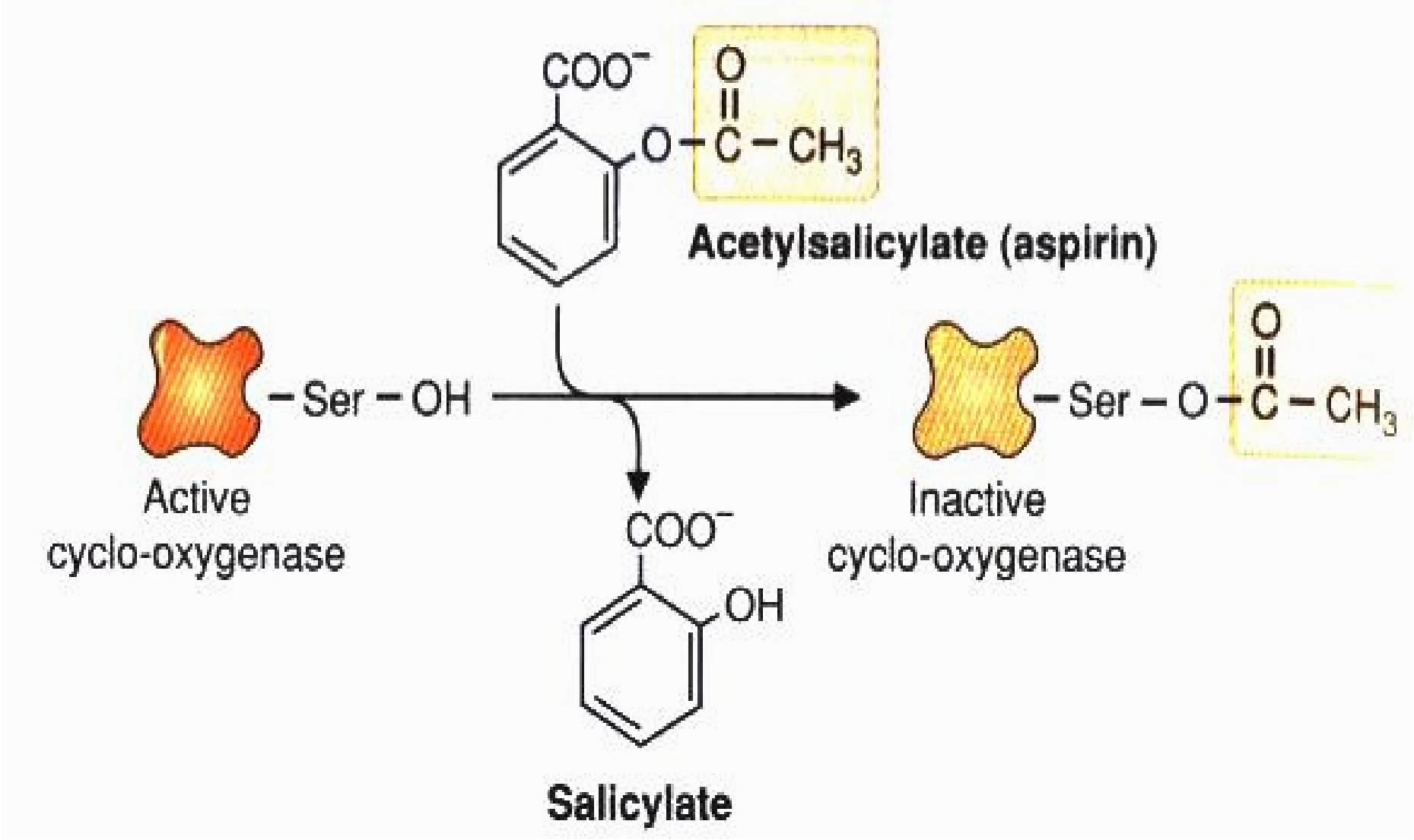
- Bradykinin and Histamine can activate biosynthesis of PGE_2 in region of Hypothalamus where body temperature is regulated, causing increase body temperature or fever (**Pyrogenic effect of Prostaglandins**);

- Interleukin-1 (IL-1α) acts on Hypothalamus to cause increase production of Prostaglandins, thereby increasing body temperature,
- Prostaglandins (PGE, PGA) and Prostacyclin (PGI_2) are Vasodilators,
  - They lower systemic arterial pressure, thereby increasing local blood flow and decreasing peripheral resistance,

State sites of action of inhibitors of Prostaglandin biosynthesis

- Some therapeutic drugs that affect biosynthesis of Prostaglandins:
- **NSAIDs** (examples):
  - Aspirin,
  - Indomethacin,
  - Phenylbutazone,
- They block biosynthesis of Prostaglandin by irreversibly inhibiting **COX** (See **Figs: 4 & 6**),
- **Aspirin, inhibition occurs by Acetylation of COX,**

Fig. 6: Action of Aspirin: Acetylation of active site of Cox



- **Steroidal Anti-inflammatory Drug**:
  - Corticosteroid blocks Prostaglandin production by inhibiting action of PLA_2
    - It affects mobilization of Arachidonic acid, which is substrate for COX (**Figs 4 & 6**),

- Factors that control biosynthesis of Prostaglandins are poorly understood, but, in general:
  - Prostaglandin release is 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,

REFERENCES

- Textbook of Biochemistry with Clinical Correlations 4th Edition. Edited by Thomas M. Delvin. Chapter on Steroid Hormone.
- Harper's Illustrated Biochemistry 26th Edition; 2003; Ed. By R. K. Murray et. al.
- Biochemistry, By V. L. Davidson & D. B. Sittman. 3rd Edition.
- Hames BD, Hooper NM, JD Houghton; Instant Notes in Biochem, Bios Scientific Pub, Springer; UK.
- VJ Temple Biochemistry 1001: Review and Viva Voce Questions and Answers Approach; Sterling Publishers Private Limited, 2012, New Delhi-110 – 020.
- G Beckett, S Walker, P Rae, P Ashby, Lecture Notes: Clinical Biochemistry 7th Ed. 2008, Blackwell Publishing, Australia.
- WWW.archway.ac.uk/activities/Departments/SHHP/
- WWW.chem.wsu.edu/Chem102/
- WWW.indstate.edu/thcme/